Mathematical models on the dogmas of HIV contagions

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Contents of My Talk

• Basics of HIV
• HIV transmission
• Mathematical Models in HIV
• Therapeutic use of IL-2
• Awareness Campaign in HIV
What is AIDS?

- **Acquired**: To come into possession of something new
- **Immune Deficiency**: Decrease or weakness in the body’s ability to fight off infections and illnesses
- **Syndrome**: A group of signs and symptoms that occur together and characterize a particular abnormality

- **HIV is the virus that causes AIDS**
- **Not everyone who is infected with HIV has AIDS**
- **Everyone with AIDS is infected with HIV**
- **AIDS is result of the progression of HIV Infection**
- **Anyone infected with HIV, although healthy, can still transmit the virus to another person**

AIDS is the final stage of the disease caused by infection with a type of virus called HIV.
Historical background of HIV/AIDS

- In 1981 AIDS was first recognized in young previously healthy homosexual men in New York City, Los Angeles and San Francisco.
- In 1983 a cytopathic retrovirus was isolated from persons with AIDS and associated condition such as chronic lymphadenopathy.
- In 1985 serological tests had been developed and licensed to make aware of verification of infectivity with HIV.
- In 1987 alteration incorporated HIV encephalopathy, wasting syndrome, and other AIDS indicator diseases were diagnosed presumptively.
- The first AIDS case in India was detected in 1986 and since then HIV infection has been reported in all states and union territories.
Structure & Manifestation of HIV Virion

[Diagram showing the structure of the HIV virion with labels for gp41, gp120, membrane, p17, p6, p24, p7, protease, integrase, reverse transcriptase, and CTL immune surveillance by cytotoxic T lymphocytes.]
HIV Infection in Target T cells

**Latent infection**
- gp120 binding to CD4
- Chemokine receptor
- Chromosomal DNA
- Proviral DNA

**Active infection**
- mRNA
- Viral RNA
- Unintegrated proviral DNA
- Budding of viruses from the host cell
- Synthesis of viral components
- Assembly of viruses
- Transcription of proviral DNA

**PRODUCTIVELY INFECTED CELL**
(Viral peptides presented to CTL)

**LATENTLY INFECTED CELL**
(No viral peptides presented to CTL)
How is HIV Transmitted?

- Unprotected sexual contact with an infected partner
- Exposure of broken skin or wound to infected blood or body fluids
- Transfusion with HIV-infected blood
- Injection with contaminated objects
- Mother to child during pregnancy, birth or breastfeeding
**HIV: A Global Pandemic**

**Adults and children estimated to be living with HIV/AIDS (2003): 34 – 46 million total**

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Europe &amp; Central Asia</td>
<td>1.2 – 1.8 million</td>
</tr>
<tr>
<td>North America</td>
<td>790 000 – 1.2 million</td>
</tr>
<tr>
<td>Caribbean</td>
<td>350 000 – 590 000</td>
</tr>
<tr>
<td>Latin America</td>
<td>1.3 – 1.9 million</td>
</tr>
<tr>
<td>North Africa &amp; Middle East</td>
<td>470 000 – 730 000</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>25.0 – 28.2 million</td>
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<tr>
<td>Eastern Europe &amp; Central Asia</td>
<td>1.2 – 1.8 million</td>
</tr>
<tr>
<td>East Asia &amp; Pacific</td>
<td>700 000 – 1.3 million</td>
</tr>
<tr>
<td>South &amp; South-East Asia</td>
<td>4.6 – 8.2 million</td>
</tr>
<tr>
<td>Australia &amp; New Zealand</td>
<td>12 000 – 18 000</td>
</tr>
</tbody>
</table>

*Source: UNAIDS*
Clinical Latency Period

- HIV continues to reproduce, **CD4** count gradually declines from its **normal value of 500-1200**.

- Once **CD4 count drops below 500**, HIV infected person at risk for **opportunistic infections**.

- **CD4 count drops below 200** person is considered to have advanced HIV disease

- If preventative medications not started the HIV infected person is now at risk for infesting secondary infections and achieving death - Most deaths occur with **CD4 counts below 50**.

- The median incubation period from HIV infection until development of AIDS is estimated at approximately 10 years for young adults.

- Without treatment, people with AIDS typically survive about 3 years.
Modeling the HIV System
Our Approach
Published papers in this field


Anti-viral drug treatment along with immune activator IL-2: a control based mathematical approach for HIV infection

- The effect of *combination of drug therapy* (Reverse Transcriptase Inhibitors (RTI) and Interleukin -2 (IL-2)).

- How the drugs act to reduce the cellular infection and simultaneously to activate the immune system?

- The effect of latently infected CD4+T cell population and the effect of IL-2 therapy.

- The control effectiveness of RTI and IL-2 in different approaches.

- The effectiveness of the drugs to make an impact on the immune system.

- The effect of perfect adherence to antiretroviral therapy as studied in respect of our basic mathematical model.
Formulation of the basic model as implicit form

\[
\begin{align*}
\dot{x} &= \lambda - d_1 x - (1 - \eta_1 u_1) \beta_1 x y_i + \eta_2 u_2 x \\
\dot{y}_i &= (1 - \eta_1 u_1) \beta_1 x y_i - d_2 y_i - \beta_2 y_i z + \delta y_l \\
\dot{y}_l &= \nu y_i - d_3 y_l - \delta y_l \\
\dot{z} &= s y_i - d_4 z + \eta_3 u_2 z.
\end{align*}
\] (1)

The work has been published in “International Journal of Control, Vol. 85, No. 2, February 2012, 220-237”
Drug therapy with perfect adherence in explicit form

\[
\begin{align*}
\frac{dx}{dt} &= \lambda - d_1 x - \beta_1 x y_i - p_1 x R + q_1 x I, \\
\frac{dy_i}{dt} &= \beta_1 x y_i - d_2 y_i - \beta_2 y_i z - p_2 y_i R + \delta y_i I, \\
\frac{dy_l}{dt} &= \nu y_i - d_3 y_l - \delta y_l I, \\
\frac{dz}{dt} &= s y_i - d_4 z + q_2 z I, \\
\frac{dx'}{dt} &= p_1 x R - d_1 x', \\
\frac{dy_i'}{dt} &= p_2 y_i R - d_2 y_i'.
\end{align*}
\]

Here \( R(t) \) and \( I(t) \) denotes the drug concentration in the plasma of RTIs and IL-2 respectively. The dynamics of the drugs are given by:

\[
\begin{align*}
\frac{dR}{dt} &= -d_R R, \quad t \neq t_k \\
\frac{dI}{dt} &= -d_I I, \quad t \neq T_l.
\end{align*}
\]

\[
\begin{align*}
\Delta R &= R_d, \quad t = t_k \\
\Delta I &= I_d, \quad t = T_l.
\end{align*}
\]
Numerical Simulation of both explicit and implicit model

Figure 2. The system behaviour for without control ($u_1 = 0$, and $u_2 = 0$) and with control ($u_1 = 0.5$ and $u_2 = 0$).
Numerical Simulation of both explicit and implicit model

Figure 3. The system behaviour for without control \((u_1 = 0, \text{ and } u_2 = 0)\) and with control \((u_1 = 0 \text{ and } u_2 = 0.025)\).
Figure 4. The system behaviour for without control ($u_1 = 0$, and $u_2 = 0$) and with control ($u_1 = 0.5$ and $u_2 = 0.025$).
Figure 5. The system behaviour for the optimal treatment schedule of the control variable $u_1(t)$ and $u_2(t)$ for $P=10, Q=18$ (left panel), and for $P=15$ and $Q=18$ (right panel).
Figure 6.6: The impulsive system behaviour for the perfect adherence with $R_d = 5$, $I_d = 7$ and $\tau = \sigma = 0.2$. Inset: Trajectories for the system in absence of therapy.
Figure 6.7: The impulsive system behaviour for the perfect adherence with $R_d = 5$, $I_d = 7$ and $\tau = \sigma = 0.5$. Inset: Trajectories for the system in absence of therapy.
Discussions

• During the disease progression the antigenic response of the body is totally collapsed. Thus, only RTIs can not totally control the disease.

• Far better results will appear using immune activator IL-2, compared to only using of RTIs, because IL-2 stimulate the immune system to act properly.

• Fixed dosing interval (dosage interval for IL-2) if RTIs are taken with sufficient frequency. The infected CD4T cell population approaches towards extinction.

• If the drug dosage are taken with perfect adherence on considering the derived condition of drug doses interval and drug dosage, then cellular infection can be controlled and immune system acts properly.
Human awareness results in the reduction of susceptibility to infection, naturally, in the epidemiological study this factor should be included.

Research reveals that most HIV infections come from undiagnosed people and untreated people, but principally from unaware people.

Broadcast media have tremendous reach and influence, particularly with young people, so in this study, we incorporate the influence of media and investigate the effect of awareness program in disease outbreaks.

In this present study, we have analyzed a simple SI network epidemic model to study the impact of awareness programs conducted through media campaigning on the spread of HIV/AIDS in a variable population with immigration. However, these results will fall into the non-network epidemic models category.
We consider a basic HIV model

\[
\frac{dS}{dt} = \Pi - \beta SI - dS,
\]

\[
\frac{dI}{dt} = \beta SI - (d + \delta I)I,
\]

(1)

where \(S(t)\) and \(I(t)\) are the densities of the susceptible and infected populations, respectively, in the region under consideration at any time \(t\). Therefore, the total population is \(N(t) = S(t) + I(t)\). \(\Pi\) is the constant recruitment rate in the susceptible population either by birth or immigration; \(\beta\) is the disease transmission rate; \(d\) is the natural death rate of

On the basis of the above assumptions, system (1) reduces to

\[
\frac{dS_-}{dt} = \Pi - \beta S_- I_- - \alpha_1 S_- M + \lambda_1 S_+ - dS_-,
\]

\[
\frac{dS_+}{dt} = \alpha_1 S_- M - \lambda_1 S_+ - dS_+,
\]

\[
\frac{dI_-}{dt} = \beta S_- I_- - \alpha_2 I_- M + \lambda_2 I_+ - (d + \delta I)_- I_-,
\]

\[
\frac{dI_+}{dt} = \alpha_2 I_- M - \lambda_2 I_+ - (d + \delta I)_+ I_+,
\]

\[
\frac{dM}{dt} = \eta I_- - \eta_0 M
\]

with the initial conditions \(S_-(0) = S_0-, S_+(0) = S_0+, I_-(0) = I_0-, I_+(0) = I_0+, M(0) = M_0\),

where \(\alpha_i (i = 1, 2)\) is the contact rate between unaware individuals and media.
Figure 1  Variations of populations with time.

Figure 2  Non-linear stability of \((S^*, I^*)\) in \(S^* - I^*\) plane.
Figure 3  Non-linear stability of $(S_+^*, I_+^*)$ in $S_+^* - I_+^*$ plane.

Figure 4  Variation of infected population and other populations with different values of $\lambda_1$. 

\[
\begin{align*}
S_-(t) & \quad 400 \\
S_+(t) & \quad 200 \\
I_-(t) & \quad 50 \\
I_+(t) & \quad 500 \\
M(t) & \quad 10 \\
\end{align*}
\]
Figure 5 Variation of infected population and other populations with different values of $\lambda_2$.

Figure 6 Awareness performance for different values of media campaign, $M_0$ under high infection scenario ($0.002 < \beta < 0.007$).
Figure 7 The system behavior for optimal control when final time is $t_f = 1$ (keeping all other parameters same as before considered).

Figure 8 Optimal control parameters $u_1^*$ and $u_2^*$ are plotted as the functions of time, keeping all other parameters same.
In the modeling process, it is assumed that media campaigns create awareness regarding personal protection as well as control AIDS.

Individuals of this class not only protect themselves from the infection, but being aware they also take part in reducing AIDS by taking precautions.

Awareness programs reduce the infection rate, shorten the rate of disease transmission and cut down the size of the disease.
The book discusses different therapeutic approaches based on different mathematical models to control the HIV/AIDS disease transmission. It uses clinical data, collected from different cited sources, to formulate the deterministic as well as stochastic mathematical models of HIV/AIDS. It provides complementary approaches, from deterministic and stochastic points of view, to optimal control strategy with perfect drug adherence and also tries to seek viewpoints of the same issue from different angles with various mathematical models to computer simulations. The book presents essential methods and techniques for students who are interested in designing epidemiological models on HIV/AIDS. It also guides research scientists, working in the periphery of mathematical modeling, and helps them to explore a hypothetical method by examining its consequences in the form of a mathematical modeling and making some scientific predictions.

The model equations, mathematical analysis and several numerical simulations that are presented in the book would serve to reveal the consequences of the logical structure of the disease transmission, quantitatively as well as qualitatively. One of the chapters introduces the optimal control approach towards the mathematical models, describing the optimal drug dosage process that is discussed with the basic deterministic models dealing with stability analysis. Another one chapter deals with the mathematical analysis for the perfect drug adherence for different drug dynamics during the treatment management. The last chapter of the book consists the stochastic approach to the disease dynamics on HIV/AIDS. This method helps to move the disease HIV/AIDS to extinction as the time to increase. This book will appeal to undergraduate and postgraduate students, as well as researchers, who are studying and working in the field of bio-mathematical modeling on infectious diseases, applied mathematics, health informatics, applied statistics and qualitative public health, etc. Social workers, who are working in the field of HIV, will also find the book useful for complements.
Thank You!