Original article:

Comparative Study of Transmission and Control of HIV/AIDS in Pakistan

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Abstract:

Background: HIV/AIDS is nowadays considered as the greatest public health disaster of modern time. It has become the challenge for the global population for decades. ***Method:*** In our study, we shall emphasize on comparative study which coordinates the field of health awareness activities on the basis of educational and informational campaigns. ***Result:*** For this purpose we generate a mathematical model having two susceptible classes depending on changes in behavior with educational activities. ***Conclusion:*** We shall try to create stability between the numbers of infected individuals and the cost of the education campaign using optimal control theory.

Keywords: HIV/AIDS; optimal control theory; educational activities; comparative study; Pakistan.

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Introduction

HIV/AIDS is responsible for 2.8 million deaths in a single year and persistent suffering in its 38.6 million present victims [1].It has become the challenge for the global population for decades. Tirmizi has developed spatial multilevel models which described and estimated the HIV/AIDS epidemic in different regions of Pakistan. Variation of infection rate in the eight cities of Pakistan was very prominent in those models. Spatial effects significantly minimized the random variability in HIV occurrence from corner to corner of the cities. Thus, these models are relatively exact and provide a precise map of the division of HIV incidence in Pakistan[2].

We have studied about several techniques, which can be applied to improve the treatment of HIV/AIDS. We also studied the side effects of ARV treatment, including diabetes mellitus, insulin resistance, dyslipidemias and Lacticacidosis associated with NRTI mitochondrial toxicity and the lipodystrophy syndrome[3]. Our plan is to support doctors gain a practical knowledge of these side effects, with the goal of improving the tolerability and efficacy of HIV treatment, helping the early diagnosis and minimize severe side effects of the drug.

All these efforts seem useless without cooperation of patient. In 2010, four treatment centers were established in major cities like Karachi, Lahore, Peshawar and Islamabad of Pakistan. These centers were arranged to make treatment of HAART available to 8000 infected people free of cost. It is surprising to know that only hundred patients are registered up to now. Infected people are very unwilling to visit such centers because they feared to be looked down upon by the society.

While Pakistan is a developing country and Pakistan's per capita income is up to $1,513. Anti-retroviral drugs (ARV) are very expensive, and the majority of the world's infected individuals including Pakistani's cannot afford medication and treatment for HIV and AIDS at their own level. The cost of standard treatment is approximately $300–500, (Rs.30,000-50,000) per year in Pakistan. Therefore, there is a need of alternate solution to acquire optimal results.

Literacy rate of Pakistan is just fifty five percent that is very lowest in the world. Therefore, in our research we have emphasized on comparative study which coordinate the field of protective activities

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on the basis of educational and informational campaigns. The health educational projects about HIV, can enhance awareness, improves integrity into society and helps family solidarity. Government and nongovernmental interventions in Pakistan should begin flash campaigns to give information and educational materials to the people about the preventive measures of the disease. Then this emphasis can move towards the treatment campaigns that will be great achievement in decreasing the new HIV infections.

In this study we are going to generate a mathematical model having two susceptible classes depending on changes in behavior with educational activities.

Preliminaries

As we have explained above, mathematical models are used in comparing, forecasting, applying, estimating and optimizing a number of findings, prevention and treatment and control programs [4]. We introduce the given below definitions and theorems necessary to optimize the model of HIV/AIDS.

Optimal Control Method:

Optimal control theory is being used as a mathematical tool in decisions making about complex biological situations and it is a part of calculus of variations. Optimal control methods are used in generating and evaluating optimal strategies to control many types of infectious diseases [5]. For example, it can be used to calculate the percentage of the population in time base epidemic model to lessen the infected people and the cost of treatment policy.

The performance of a dynamic system is defined by the state variable (s). We assume that we can control state variable‘s’ by applying a suitable control ‘x’. We observed that the dynamic system (state x) be subject to another control u. We can generate minimize or maximize objective function $J(u(t), x(t), t)$ by adjusting the control that achieves the preferred goal, and the required costs to attaining it. The optimal control is acquired when the preferred objective is attained with the minimum cost. The functions depend on the state variable ’x’ and the control ’u’. Even though There are different techniques for estimating the optimal control for a particular model but Pontryagin Maximum Principle is very specific and gives us the best calculation of the optimal control for the ordinary differential equations model with constraints [5].

An optimal control problem showed the following properties:

(i) Controllability: capability to use controls to direct a system from one point to another.
(ii) Observability: assuming system info from control input and observe output.
(iii) Stabilization: applying controls towards force stability.

The main purpose of the optimal control problem is to give solution with some initial conditions that need to fulfil by an optimal control and related state. We are going to explain the logical difference between the necessary and sufficient conditions of solution sets.

Considering the following optimal control problem:

$$\min_{u}\{\emptyset\left(t_f, x(t_{f,})\right) + \int_0^{t_{f,}} g_o\left(t, x(t), u(t)\right)dt\} \quad (1)$$

Where state vector is

$f\left(x(t)\right) = [x_1(t), x_2(t), \dots \dots \dots x_n(t)]^T \in R^n$

And the control vector is.

$\left(u(t)\right) = [u_1(t), u_2(t), \dots \dots \dots u_n(t)]^T \in R^m$

The state and the control variables are directed by the ordinary differential equations of first order:

$$\frac{dx}{dt} = f\left(t, x(t), u(t)\right) \quad (2)$$

$$x_o = x(0), 0 \le t \le t_f$$

The functions given below are differentiable w.r.t. every component of x and u, and piecewise continuous w.r.t.’t’.

$f(h_o): T \times R^n \times R^m \rightarrow R^n$

$f(g_o): T \times R^n \times R^m \rightarrow R^n$

Pontryagin’s Maximum Principle:

The Pontryagin’s Maximum Principle is used to change the objective function of maximization or minimization with the state variable ‘x’ into pointwise maximizing or minimizing of the Hamiltonian w.r.t the control.

The Hamiltonian $H(t, x, u, \lambda)$ is a four variables function where x and u are functions of ‘t’ While λ is an adjoint variable with function of t.

Theorem 1. There exists a piecewise differential adjoint variable $\lambda(t)$ whenever $u^*(t)$ and $x^*(t)$ are optimal, such that

$H(t, x^*(t), u(t), \lambda(t)) \le H(t, x^*(t), u^*(t), \lambda(t))$; $\forall u$

Where the Hamiltonian H is

$$H = f(t, x(t), u(t)) + \lambda(t)g(t, x(t), u(t))$$

And

$$\frac{\lambda(t)}{dt} = -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x}$$

$$\lambda(t_f) = 0$$

.

Necessary conditions: If $u^*(t)$ and $x^*(t)$ are optimal, then the below conditions must satisfy:

$$\frac{\lambda(t)}{dt} = -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x}$$

$$\lambda(t_f) = 0,$$

Then $\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial u} = 0$.

Sufficient conditions: $u^*(t), x^*(t)$ and $\lambda(t_f)$ fulfil the below conditions:

$$\frac{\lambda(t)}{dt} = -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x}$$

$$\lambda(t_f) = 0,$$

$$\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial u} = 0$$

,

is sufficient for $u^*(t)$ and $x^*(t)$ are optimal.

Sensitivity analysis:

Sensitivity analysis is used to decide whether the infectious disease will spread in the population or not. We perform the analysis by calculating the sensitivity indices of the basic reproduction number R_o.In the sensitivity analysis, we apply the normalized forward sensitivity index of a variable which is defined as

$$r_k^{j_o} := \frac{\partial J_o}{\partial k} \times \frac{k}{J_o} \quad (3)$$

Where is an invariant J depends on a parameter 'k'.

Brownian motion

R. Brown is defined the perpetual, irregular random motion of small particles absorbed in a liquid or gas, which is known as Brownian motion. The molecules of the surrounding medium can be explained by perpetual collisions of the particle. The stochastic process linked with the Brownian motion is called the Brownian process. Thus Brownian motion is playing important role in the field of modern quantitative finance. Definitely, the simple continuous time model for financial asset prices assumes that the log-return of a known financial asset explained by a Brownian motion. It has a lot of interesting application in epidemiology[6].

Definition: Consider a probability space $(\Omega, F, P)$with filtration$\{F_t\}_{t \geq t0}$. Brownian motion which is a real valued continuous function $\{F_t\}$ with the modified process $\{B_t\}_{t \geq t0}$has the following characteristic:

(i) $B_o = 0$;

(ii) $0 \leq s < t < \infty$, then $B_t - B_s$ is normally distributed with zero mean and variance equal to t-s;

(iii) $B_t - B_s$ is independent of $\{F_s\}$ for $0 \leq s < t < \infty$;

(iv) $t \geq 0$, B_t is continuous.[4]

The multi-dimensional $\widehat{\text{Ito}}$'s formula

Let $x(t)$ be a $\widehat{Ito}$'s process of d-dimensionalon $t \geq 0$ with the stochastic differential [5].

i.e., a stochastic process of the form:

$$dx(t) = f(t)dt + g(t)dB(t) \quad (4)$$

Where $f \in L^1(R+; R^d) and g \in L^2(R+; R^{d \times m})$.

Then any $V(x(t),t)$ is again an Ito's process with the stochastic differential, which is given by

$$dV(x(t),t) = \left[V_t(x(t),t) + V_x(x(t),t)f(t) + \frac{1}{2}trace\left(g^T(t)V_{xx}(x(t),t)g(t)\right) + V_x(x(t),t)g(t)dB(t)\right] \tag{5}$$

Note that
$dtdt = 0, dB(t_i)dt = 0, dB_i dB_i = dt, dB_i dB_j = 0 \; if \; i \neq j.$

Stability in probability theory

Consider the general stochastic system:
$dx(t) = f(t,x(t))dt + g(t,x(t))dB(t)$

for $t \geq 0$ with primary conditions $x(0) = x_o$. The solution is indicated by $x(t,x_o)$.

Assume that $f(t,0) = g(t,0) = 0; \; \forall \; t \geq 0$, the equilibrium x = 0 of the system is supposed to be:

(i) Probabilistic Stable; $\forall \in > 0$, if

$\lim_{x_o \to x} P\left(\sup_{t \geq 0} |x(t,x_o)| \geq \in\right) = 0$ (ii) Exponentially stable; $\forall \, x_o \in R^n$ if

$\lim_{x_o \to x} \left(supn \frac{1}{t} ln|x(t,x_o)| < 0\right)$

Differential Operator

The equation of the differential operator L:
$dx(t) = f(x(t),t)dt + g(x(t),t)dB(t) \; t \geq t_o,$

By

$$L = \frac{\partial f(x(t),t)}{\partial t} + \sum_{I=1}^{d} f(x,t)\frac{\partial}{\partial x_i} + \frac{1}{2}\sum_{i,j=1}^{d}[g(x,t)g^T(x,t)]_{i,j}\frac{\partial^2}{\partial x_i \partial x_j}.$$

If apply L on a function $V \in C^{2,1}(S_h \times R_+; R_+)$, then

$LV = V_t(x,t) + V_x(x,t) + \frac{1}{2}trace[g^T(x,t)V_{xx}(x,t)g(x,t)]$, where

$V_t = \frac{\partial V}{\partial t}, Vx = \frac{\partial V}{\partial x_1}, \ldots, \frac{\partial V}{\partial x_d}, \; Vxx = \left(\frac{\partial^2 V}{\partial x_i \partial x_j}\right)_{d \times d}$

In the next section, we formulate our model and discuss briefly about its stability analysis.

An Optimal Control Mathematical Model

We are going to develop an optimal control model for HIV/AIDS with HIV prevention mass media campaigns and withdrawal of individuals with AIDS. These campaigns are offered to dividing susceptible into two subclasses, namely S and s_1, where s_1 is the class who has decided to change their activities due to an effective educational campaign. Consequently class s_1 has lesser transmission rates than the susceptible class S. Consider an optimal control ordinary differential equation model:

$$\begin{aligned}
s'(t) &= -(t_{r_1} + t_{r_2})E(t)s(t) - \alpha_1 s(t)J(t) + \Lambda - ds(t) \\
s_1'(t) &= t_{r_1}E(t)s(t) - \alpha_2 s_1(t)J(t) - ds_1(t) \\
J'(t) &= \alpha_1 s(t)J(t) + \alpha_2 s_1(t)J(t) + dJ(t) - \delta J(t) \\
A'(t) &= (\mu + \delta)A
\end{aligned} \tag{6}$$

With initial condition $s(0), s_1(0), J(0)$ and $A(0)$

All parameters in the model are positive. While $N = s + s_1 + J + A$

Where

$s(t) =$ Susceptible class

$s_1(t) =$ Susceptible class those have changed their behavior educational activities about HIV/AIDS.

$J(t) =$ HIV positive individuals are sexually active.

$A(t) =$ Aids patients

$E(t) =$ Educational activities about HIV/AIDS program.

$t_{r_1}, t_{r_2} =$ Transfer rate to the educated susceptible classes

$\alpha_1, \alpha_2 =$ Infection rate

Its feasible region is

$\omega = \{s(t), s_1(t), J(t), A(t) \epsilon R^4; 0 \le N(t) \le \frac{\alpha}{d}\}$

Where $N = s + s_1 + J + A$

Also $N'(t) = \wedge - dN(t)$

Its solution is

$$N(t) = N(0)e^{-dt} - \frac{\wedge}{d}\left(1 - e^{-dt}\right)$$

If $t = 0 N(0) = \frac{\wedge}{d}$

Thus every solution of the model (6) with initial values will remain in invariant region;

Then the objective function

$z = \int_0^T [E^2 + A(s + s_1) + J]dt$; $0 \le z(t) \le \alpha \le 1$,

Where α is the treatment rate and taking E in square form to ensure convexity of the problem. Our problem is of minimization i.e. minimizing the infected population which means increase the susceptible population. Where both objective function and equations (6) are linear in this control system and one can see that there exist an optimal states and control.

For optimal control, we require to drive basic conditions.

By using Pontryagin's maximum principle, the Hamiltonian for this problem is stated as

$$H(t, s, s_1, J, A, \lambda_1, \lambda_2, \lambda_3, \lambda_4) = E^2 + A(s + s_1) + J + \lambda_1\{-(t_{r_1} + t_{r_2})E(t)s(t) - \alpha_1 s(t)J(t) + \Lambda - ds(t)\} + \lambda_2\{t_{r_1}E(t)s(t) - \alpha_2 s_1(t)J(t) - ds_1(t)\} + \lambda_3\{\alpha_1 s(t)J(t) + \alpha_2 s_1(t)J(t) + dJ(t) - \delta J(t)\} + \lambda_4(\mu + \delta)A \tag{7}$$

For a given E^* (optimal control), s^*, s_1^*, J^* and A^* be the optimal solution are given for the optimal control problem. Then the costate variables satisfying the below equations

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= -[A + \lambda_1\{t_{r_1}E(t) - t_{r_2}E(t) - \alpha_1 J(t) - d\} + \lambda_2 t_{r_1}E(t) + \lambda_3\alpha_1 J(t)] \\
\frac{d\lambda_2}{dt} &= -[A + \lambda_2\{-\alpha_2 J(t) - d\} + \lambda_3\alpha_2 J(t) \\
\frac{d\lambda_3}{dt} &= -\{1 + \lambda_1(-\alpha_1 s(t)) + \lambda_2(-\alpha_2 s(t)) + \lambda_3(\alpha_1 s(t) + \alpha_2 s_1(t) - d - \delta)\} \\
\frac{d\lambda_4}{dt} &= \lambda_4(\mu + d)
\end{aligned} \tag{8}$$

With the transversally properties

$\lambda_1(t) = \lambda_2(t) = \lambda_3(t) = \lambda_4(t) = 0$

And the optimal control adopts the form

$$E^*(t) = \min\left[\max\left(\frac{(\lambda_1 - \lambda_2)t_{r_1}s(t) + \lambda_1 t_{r_2}s(t)}{2}, \alpha\right)\right] \tag{9}$$

Proof: Using Pontryagin maximum principle, we have to calculate partial derivative of the Hamiltonian w.r.t state variable. Since the basic conditions hold:

$$\frac{d\lambda_4}{dt} = \lambda_4(\mu + d)$$

Integrating

$\lambda_4 = m_1 e^{(\mu+d)t}$; m_1 is constant.

Since $\lambda(t) =$ 0 Then $\lambda_4 = 0$

Now calculate $-\frac{\partial H}{\partial s}, -\frac{\partial H}{\partial s_1}, -\frac{\partial H}{\partial J}$ and $-\frac{\partial H}{\partial A}$ and get the equations stated in theorem statement.

Since Hamiltonian is minimized w.r.t the control variable at E* i.e.

$$\frac{\partial H}{\partial E} = 2E - \lambda_1(t_{r_1} + t_{r_2})s(t) + \lambda_2 t_{r_1}s(t) \tag{10}$$

$= 2E - (t_r\lambda_1 - t_r\lambda_2)s(t)$

Either $\frac{\partial H}{\partial E} < 0$ or > 0

Now if

$$2E - \lambda_1(t_{r_1} + t_{r_2})s(t) + \lambda_2 t_{r_1}s(t) = 0$$

For some value of [0, α]

Then we can say given value of E is optimal.

Also

$$2E - \lambda_1(t_{r_1} + t_{r_2})s(t) + \lambda_2 t_{r_1}s(t) \geq 0$$

$$2E - \lambda_1(t_{r_1} + t_{r_2})s(t) + \lambda_2 t_{r_1}s(t) \leq 0$$

Then we must have

$$E^*(t) = \min\left[\max\left(\frac{(\lambda_1 - \lambda_2)t_{r_1}s(t) + \lambda_1 t_{r_2}s(t)}{2}, \alpha\right)\right]$$

Thus $E_1^*(t)$ also must optimize H and by a related argument we get the certain expression for $E_1^*(t)$.

Simulation results of optimal control Model

Optimal control system is solved by R K method order 4, the illustration of results with numerical solutions is carried out by using Berkeley Madonna.

The value of Parameters has been taken from HIV/AIDS Surveillance Reports Pakistan.

Parameters	Description	Values
$s(t)$	Susceptible class	0.1
$s_1(t)$	Susceptible class those have changed their behavior by educational activities about HIV/AIDS.	0.85
$J(t)$	HIV positive persons who are sexually active.	0.058
$E(t)$	Educational activities about HIV/AIDS program.	1.95
t_{r_1}, t_{r_2}	Transfer rate to the educated susceptible classes	0.001,0.0015
α_1, α_2	Infection rate	0.0019,0.0152
μ	Death rate	0.085
D	Disease related death rate	0.073
Λ	Recruitment rate	0.005
A	Individual with AIDS	0.02

Table 1. Parameters values with their description used in the above model.

Numerical result in figure 1 (a) shows that initially susceptible class increased after health awareness activities and optimal control treatment. In figure 1 (b) we observed that population of infected class is sharply increased without health education activities. This shows that we required treatment and health awareness. In figure 1 (c), it is observed that number of infected individuals is decreased due to optimal control system also decrease in AIDS individuals as well. Thus we conclude that we can control new infected class by propagation of control treatment and health disease awareness programs.

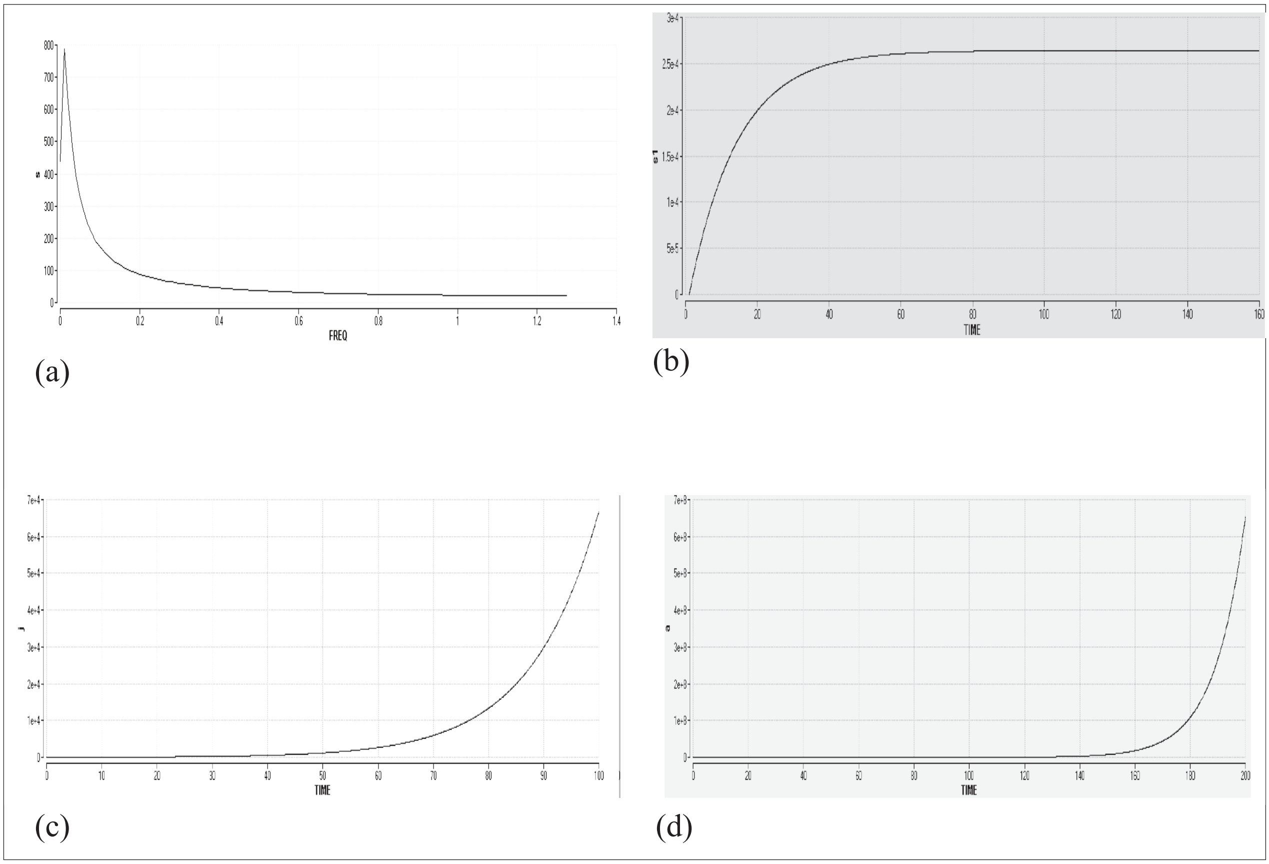

Figure 1. Simulation results of optimal control model.

<u>Conclusion</u>

In our study,we highlighted the fact that optimal control system plays an important role to understand transmission dynamics of epidemics and predicting epidemics transmission.It was observed that number of infected individuals decreased due to optimal control system which also reduced the number of AIDS individuals as well. Thus, we concluded that we could control new infected class by propagation of control treatment and health disease awareness programs and the awareness to disease couldhelp people to adopt suitable preventive procedures to keep themselves away from the risk.

Author contributions:

Data gathering and idea owner of this study: Syed Rizwan Ul Haq Tirmizi ,Nasiruddin Khan, Syed Talha Tirmizi.

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