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MATHEMATICAL MODELING APPLIED TO UNDERSTAND THE HOST-PATHOGEN INTERACTION OF HIV INFECTION IN BANGLADESH

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Abstract. The most urgent public health problem today is to devise effective strategies to minimize the destruction caused by the AIDS epidemic. The understanding of HIV infection through mathematical modeling have made a significant contribution. The interaction of host to pathogen have been determined by fitting mathematical models to experimental data. In Bangladesh, the increasing rate of HIV infection comparing to the other countries of the world is not so high. Among the most at risk population of Bangladesh the HIV prevalent is still considered to be low with prevalence $< 1\%$. In this paper, the current situation of HIV infection in Bangladesh have been shown and a mathematical representation of HIV has been discussed. We have determined the basic reproduction number R_0 and shown the local and global stability at disease free and chronic infected equilibrium points. Also we have shown that if the basic reproduction number $R_0 \leq 1$, then HIV infection is cleared from T cell population and it converges to disease free equilibrium point. Whereas if $R_0 > 1$ then HIV infection persists.

1 Introduction

Host-pathogen interactions are the interactions taking place between a pathogen (e.g. virus, bacteria) and their host (e.g. humans, plants). Host-pathogen interactions can be described on the population level (virus infections in a human population), on the organismal level (e.g. virus infects host), or on the molecular level (e.g. virus protein binds to receptor on human cell [22]. HIV stands for human immunodeficiency virus. The virus attacks the immune system, and weakens our ability to fight infections and disease. HIV/AIDS progresses in body slowly and its symptoms are

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shown after 6-8 years sometimes even later. At present, the most burning issue at the same time the most dangerous phenomena is Human Immunodeficiency Virus (HIV) [8]. Approximately 36.9 million people were living with HIV in the world at the end of 2015 [21]. Acquired Immunodeficiency Syndrome (AIDS) was first discovered in 1981 since then it has been considered as the most leading cause of mortality [6]. A detailed background and survey on HIV/AIDS is described in [3, 4, 7, 9]. HIV mainly targets CD4+ T cells. The continuous attack HIV causes the depletion of CD4+ T cells and this leads people to gradually become a victim of Acquired Immunodeficiency Syndrome (AIDS). For this reason the count of CD4+ T cells is considered as the primary indicator of progression of HIV. In recent times, mathematical modeling has become the most powerful tools to incorporate the dynamic behaviors of infectious diseases. Mathematical modeling is basically referred to as a method of simulating real-life situations with mathematical equations to forecast their future behavior [5]. Mathematical models have become the most important tools in analyzing the dynamics of infectious diseases over the years. An efficient preventive and control measure of the spread of a life-threatening pathogen mainly depends on an essential understanding of the mechanisms of that pathogen. Numerous mathematical models have been developed to identify the characteristics of Human immunodeficiency virus [2]. HIV dynamic model, a set of ordinary differential equations (ODE) that describes the interaction between HIV virus and human body cells, has been proven useful for understanding the pathogenesis of HIV infection and developing treatment strategies [13]. In this paper, we have shown the present scenario of HIV/AIDS in Bangladesh. Also we have studied a three compartmental HIV model and investigated their stability at disease free and endemic equilibrium points.

2 HIV Scenario in Bangladesh

Since the discovery of Acquired Immunodeficiency Syndrome (AIDS) in the early 1980s, this pandemic disease has spread in successive waves to the most regions of the world. To be practical mankind has never faced such a devastating pandemic disease. Although Bangladesh is still considered to be a low responded HIV infected country in world, the present situation indicate that the influence of this pandemic disease is gradually increasing. The main reason for this low prevalence could be the early and sustained HIV prevention programs targeting high risk groups backed by a state-of-the-art surveillance system. Another contributing protective factor could be the high rates of male circumcision. There is, however, a concentrated HIV epidemic among injecting drug users (IDU), primarily due to sharing of unclean syringes and needles. As a result, the rate of new infections is still on the rise and Bangladesh is the only country in the South Asia Region where new infections are rising [20]. In Bangladesh, the first case of HIV was detected in 1989. Since then, it

has been enhanced considerably. In 2015 (December 2014 to November 2015), the number of newly HIV infected people is 469 and the number of HIV/AIDS related death is 95. Till December 2015, there were 4143 reported cases of HIV and among them 658 died [21]. Here we show a graphical representation of HIV surveillance of Bangladesh (see Figure 1 and Figure 2) from 1989 to 2015 (except 2008) [20].

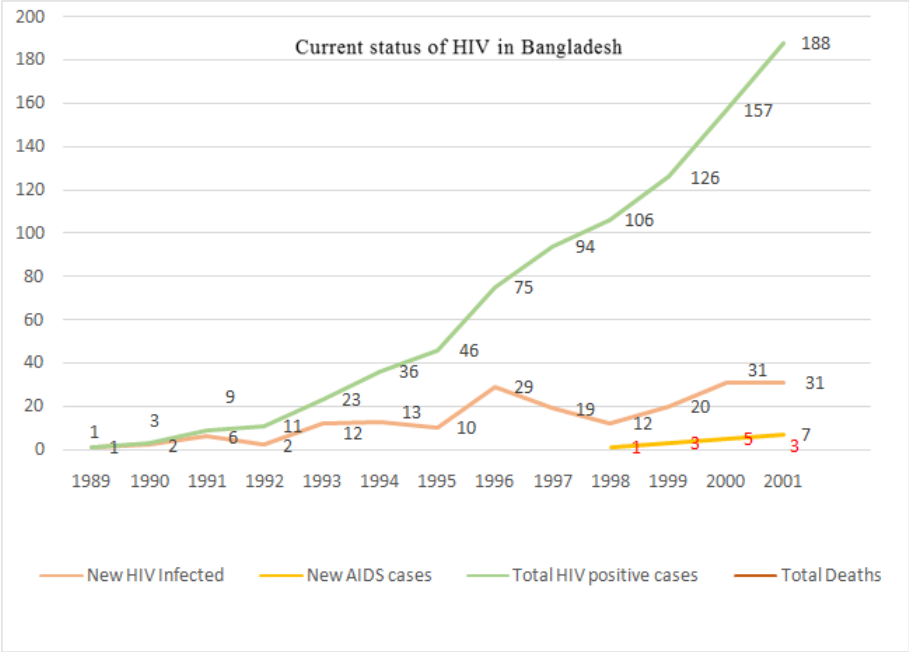

Figure 1: Number of HIV and AIDS cases from 1989-2001.

3 Mathematical Model for HIV

To generate a realistic model of T cell infection by HIV, we first need to consider the population dynamics of T cells in the absence of HIV. Our interest is to present a mathematical model of HIV infection and analyze the model. In this paper, we present a three compartmental model of HIV which has been taken from [19]. This model was also used for other countries to describe the dynamic behavior of HIV/AIDS disease. We have modified this model and added a drug efficacy parameter ϵ whose value is in the range between [0, 1] [1]. The total population size N is divided into three stages of HIV/AIDS progression; the susceptible population S, HIV infected individuals I and HIV virus V. The total population is given by $N(t) = S(t) + I(t) + V(t)$. The population CD4+ T cells starts with a source or production rate Λ and dead cells with rate α are reduced from the susceptible class. It has a logistic growth with $rS(1 - \frac{S+I}{S_{max}})$ where r is the proliferation rate. Average

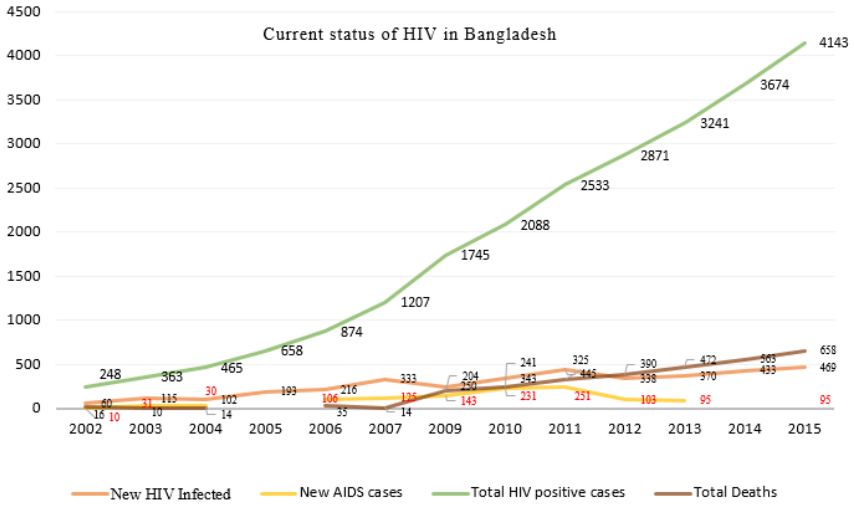

Figure 2: Number of HIV and AIDS cases from 2002-2015 (except 2008).

number of virus cells produced are N. Parameters α, β, γ are the natural turnover rates of uninfected CD4+ T cells, infected CD4+ T cells and virus, whereas S_{max} is the maximum level of CD4+ T cell concentration in the body [17]. The infected CD4+ T cell has an infection rate which is denoted by μ. The transfer diagram of the model is shown in Figure 3.

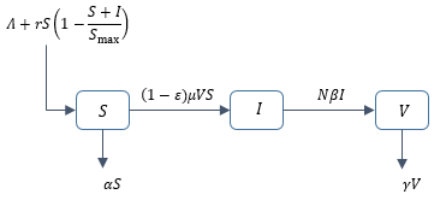

Figure 3: Transmission diagram of three compartmental HIV model.

Our modified model is governed by the following ordinary differential equations:

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \alpha S + rS(1 - \frac{S+I}{S_{max}}) - (1-\epsilon)\mu VS, \\ \frac{dI}{dt} &= (1-\epsilon)\mu VS - \beta I, \\ \frac{dV}{dt} &= N\beta I - \gamma V. \end{aligned} \tag{3.1}$$

The model is positively invariant and bounded in the region
$\Omega = \left\{S, I, V \in \Re^3_+ : N(t) \leq \frac{\Lambda}{\mu}\right\}$.
We have determined the basic reproduction number R_0 which was first introduced by Ross (1909). It is defined in epidemiological modeling as the average number of infected individuals produced by one infected immigrant in a population which is completely susceptible [11]. Finding the basic reproduction number R_0 we can determine the endemic result of disease in populations. If $R_0 < 1$, the disease vanishes and if $R_0 > 1$, the disease spreads and goes to the endemic level.

4 Analytical Analysis of the Model

Here we investigate the positivity of the model, find out different equilibrium points, formulate the basic reproduction number and check the stability at disease free and endemic equilibrium points.

4.1 Positivity of the solutions

Here we check the positivity of each compartments such as susceptible S cells, infected I and HIV virus V. We must have the positive values of these biological compartments. To test the positivity of these biological compartments, we need the following Lemma 1.

Lemma 1. *Let $S(0) > 0$, $I(0) \geq 0$, $V(0) \geq 0 \in \Omega$ then the solutions $S(t)$, $I(t)$, $V(t)$ of the model system of equations (3.1) are positives.*

Proof. To prove the Lemma 1, we have used the system of equations of the model (3.1).

$\frac{dS}{dt} = \Lambda - \alpha S + rS(1 - \frac{S+I}{S_{max}}) - (1-\epsilon)\mu VS$,
in order to find the positivity we have, $\frac{dS}{dt} = \Lambda - \alpha$, The integrating factor is

$$IF = e^{\int \alpha dt} \geq e^{\alpha t}, \tag{4.1}$$

Multiplying both sides of (4.1) by $e^{\alpha t}$ we have,

$$d(Se^{\alpha t} \geq e^{\alpha t}\Lambda dt \tag{4.2}$$

Now integrating (4.2) we get

$$Se^{\alpha t} \geq e^{\alpha t}\frac{\Lambda}{\alpha} + c_1 \tag{4.3}$$

where c_1 is a constant.
Applying the initial condition at $t = 0$, $S(t) \geq S(0)$. Hence from (4.3),
$c_1 \geq (\frac{\Lambda}{\alpha} - S)$.
Putting the value of c_1 into (4.3), we get
$S \geq \frac{\Lambda}{\alpha} + (S - \frac{\Lambda}{\alpha})e^{-\alpha t}$ $S > 0$ at $t = 0$ and $t \to \infty$. Similarly we can find the positivity of I and V under the initial conditions. Therefore it is true that, $(S(t) > 0, I(t) \geq 0, V(t) \geq 0, \forall t \geq 0)$.

4.2 Disease free and endemic equilibrium points

The disease free equilibrium of the above HIV model (3.1) can be obtained by setting $\frac{dS}{dt} = \frac{dI}{dt} = \frac{dV}{dt} = 0$, thus we have,
$\Lambda - \alpha S + rS(1 - \frac{S+I}{S_{max}}) - (1-\epsilon)\mu VS = 0, (1-\epsilon)\mu VS - \beta I = 0, N\beta I - \gamma V = 0.$
Since we have considered the case of disease free equilibrium, hence it is very simple to assume $I = 0, V = 0$. Thus the above system reduces to,
$\Lambda - \alpha S_0 + rS_0 - \frac{rS_0^2}{S_{max}}$,
$\therefore S_0 = \frac{S_{max}}{2r}[(r-\alpha) + \sqrt{(r-\alpha)^2 + \frac{4\Lambda}{S_{max}}}]$.
Thus, the disease free equilibrium is $W_0 = (S_0, 0, 0)$.
Again for the endemic equilibrium point W^*, we find $W^* = (S^*, I^*, V^*)$, where

$S^* = \frac{\gamma}{(1-\epsilon)\mu}$, $I^* = \frac{\gamma V^*}{(1-\epsilon)\beta}$, $V^* = \frac{\Lambda\mu^2 + (r-\alpha)\gamma\mu - \frac{r}{S_{max}}\gamma^2}{\mu\gamma(\mu + \frac{r\gamma}{\beta S_{max}})(1-\epsilon)}$. Now we calculate the basic reproduction number R_0 at W_0.

4.3 Basic reproduction number R_0

Basic reproduction number plays a crucial role for analyzing the behavior of infectious diseases. It represents the average number of secondary infection caused by a single infected T cell in an entirely susceptible T cell population, throughout its period. In order to find the basic reproduction number of the model (3.1), we need to identify the classes which are relevant to each other. Form the model (3.1), we observe that the classes I and V are relevant. We find the gain and losses of I and V respectively; Now, the matrix for the gain terms;

$$\mathcal{F} = \begin{bmatrix} 0 & \beta \\ (1-\epsilon)\mu S & 0 \end{bmatrix},$$

Since basic reproduction number is to be calculated at disease free equilibrium point W_0, hence

$$\mathcal{F} = \begin{bmatrix} 0 & \beta \\ (1-\epsilon)\mu S_0 & 0 \end{bmatrix},$$

Matrix for the loss terms;

$$\mathcal{L} = \begin{bmatrix} N\beta & 0 \\ 0 & \gamma \end{bmatrix},$$

Hence the basic reproduction number is $R_0 = \rho(FL^{-1}) = \frac{(1-\epsilon)N\mu S_0}{\gamma}$.
Now we check the local stability of the model (3.1) at disease free equilibrium point W_0 and chronic infection equilibrium point W^*.

4.4 Local stability of disease free equilibrium point W_0

We investigate the local stability at disease free equilibrium point W_0 but before that we need the following theorem;

Theorem 2. *If $R_0 < 1$, the disease free equilibrium point W_0 of system (3.1) is locally asymptotically stable. If $R_0 = 1$, W_0 is locally stable and if $R_0 > 1$, then W_0 is unstable.*

Proof. To prove the above theorem, the following variation matrix is computed corresponding to equilibrium point W_0. From the model (3.1), let $x = \frac{dS}{dt}, y = \frac{dI}{dt}, z = \frac{dV}{dt}$ then the system (3.1) reduces to
$x = \Lambda - \alpha S + rS(1 - \frac{S+I}{S_{max}}) - (1-\epsilon)\mu VS, y = (1-\epsilon)\mu VS - N\beta I, z = N\beta I - \gamma V$
The Jacobian matrix of the system (3.1) is given as

$$\mathcal{J} = \begin{bmatrix} \frac{\partial x}{\partial S} & \frac{\partial x}{\partial I} & \frac{\partial x}{\partial V} \\ \frac{\partial y}{\partial S} & \frac{\partial y}{\partial I} & \frac{\partial y}{\partial V} \\ \frac{\partial z}{\partial S} & \frac{\partial z}{\partial I} & \frac{\partial z}{\partial V} \end{bmatrix},$$

$$\mathcal{J} = \begin{bmatrix} -\alpha + r(1 - \frac{S+I}{S_{max}}) - \frac{rS}{S_{max}} & -\frac{rS}{S_{max}} & (1-\epsilon)\mu S \\ (1-\epsilon)\mu V & -\beta & (1-\epsilon)\mu S \\ 0 & N\beta & -\gamma \end{bmatrix}, \tag{4.4}$$

at W_0 the Jacobian matrix is

$$\mathcal{J}(W_0) = \begin{bmatrix} -\alpha + r(1 - \frac{S_0}{S_{max}}) - \frac{rS_0}{S_{max}} & -\frac{rS_0}{S_{max}} & (1-\epsilon)\mu S_0 \\ 0 & -\beta & (1-\epsilon)\mu S_0 \\ 0 & N\beta & -\gamma \end{bmatrix},$$

Now we have to find out the characteristic equation. To do that, first we have to calculate $J(W_0) - \lambda I$ where λ is a scalar and I is identity matrix. Let $B = J(W_0) - \lambda I$,

then

$$\mathcal{B} = \begin{bmatrix} -\alpha + r(1 - \frac{S_0}{S_{max}}) - \frac{rS_0}{S_{max}} & -\frac{rS_0}{S_{max}} & -(1-\epsilon)\mu S_0 \\ 0 & -\beta & (1-\epsilon)\mu S_0 \\ 0 & N\beta & -\gamma \end{bmatrix} - \begin{bmatrix} \lambda & 0 & 0 \\ 0 & \lambda & 0 \\ 0 & 0 & \lambda \end{bmatrix},$$

$$\mathcal{B} = \begin{bmatrix} -\alpha + r(1 - \frac{S_0}{S_{max}}) - \frac{rS_0}{S_{max}} - \lambda & -\frac{rS_0}{S_{max}} & -(1-\epsilon)\mu S_0 \\ 0 & -\beta - \lambda & (1-\epsilon)\mu S_0 \\ 0 & N\beta & -\gamma - \lambda \end{bmatrix}.$$

To find out the characteristic equation we need to perform $det(B) = 0$, hence
$[-\alpha + r(1 - \frac{S_0}{S_{max}}) - \frac{rS_0}{S_{max}} - \lambda][(\beta+\gamma)(\gamma+\lambda) - (1-\epsilon)\mu\beta S_0] + \frac{rS_0}{S_{max}} \times 0 - \mu S_0 \times 0 = 0,$
$\therefore -\alpha + r(1 - \frac{S_0}{S_{max}}) - \frac{rS_0}{S_{max}} - \lambda][\lambda^2 + a_1\lambda + a_2] = 0.$
Thus, the characteristic equation is $[-\alpha + r(1 - \frac{S_0}{S_{max}}) - \frac{rS_0}{S_{max}} - \lambda][\lambda^2 + a_1\lambda + a_2] = 0,$
where
$a = \beta + \gamma$, $a_2 = \beta\gamma(1 - R_0)$.
We observe that, first root of the characteristic equation is
$\lambda_1 = -\alpha + r(1 - \frac{S_0}{S_{max}} - \frac{rS_0}{S_{max}}) < 0.$
If $R_0 > 1$, then $a_2 > 0$. Also $\gamma > (1-\epsilon)\mu S_0$. Again $a_1 > 0$, hence by Routh-Hurwitz criteria [16], W_0 locally asymptotically stable. If $R_0 = 1$, then R_0 and W_0 becomes locally stable. If If $R_0 > 1$, $a_2 < 0$ and W_0 becomes unstable. Now we investigate the local stability of endemic equilibrium point W^*. □

4.5 Local stability of chronic infection equilibrium point W^*

Now we investigate the local stability of chronic infection equilibrium point W^*. We need the following Lemma 3.

Lemma 3. *Let M be 3×3 real matrix. If $tr(M), det(M)$ and $det(M^{[2]})$ are all negative, then all of the eigenvalues of M have negative real part [10].*

Before we apply the Lemma 3, we need the following definition of second additive compound matrix.

Definition 4. *Let $A = (a_{ij})$ be an $n \times n$ real matrix. The second additive compound matrix of A is the matrix $A^{[2]} = (b_{ij})$ defined as follows [14, 18].*
$n = 2 : A^{[2]} = a_{11} + a_{22}$,
$n = 3 :$

$$\mathcal{A}^{[2]} = \begin{bmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{bmatrix}.$$

Theorem 5. *The chronic infection equilibrium point W^* of the system (3.1) is locally asymptotically stable if $R_0 > 1$*

Proof. From the equation (4.4), we have

$$\mathcal{J} = \begin{bmatrix} -\alpha + r(1 - \frac{S+I}{S_{max}}) - \frac{rS}{S_{max}} & -\frac{rS}{S_{max}} & (1-\epsilon)\mu S \\ (1-\epsilon)\mu V & -\beta & (1-\epsilon)\mu S \\ 0 & N\beta & -\gamma \end{bmatrix},$$

at chronic infection equilibrium point $W^* = (S^*, I^*, V^*)$,

$$\mathcal{J}(W^*) = \begin{bmatrix} -\alpha + r(1 - \frac{S^*+I^*}{S_{max}}) - \frac{rS^*}{S_{max}} - (1-\epsilon)\mu V^* & -\frac{rS^*}{S_{max}} & (1-\epsilon)\mu S^* \\ (1-\epsilon)\mu V^* & -\beta & (1-\epsilon)\mu S^* \\ 0 & N\beta & -\gamma \end{bmatrix},$$

$$\therefore \mathcal{J}(W^*) = \begin{bmatrix} -\overline{a} & -\frac{rS^*}{S_{max}} & (1-\epsilon)\mu S^* \\ (1-\epsilon)\mu V^* & -\beta & (1-\epsilon)\mu S^* \\ 0 & N\beta & -\gamma \end{bmatrix},$$

where $\overline{a} = \alpha - r(1 - \frac{S^*+I^*}{S_{max}}) + \frac{rS^*}{S_{max}} + (1-\epsilon)\mu V^* > 0$.
Now the second additive compound matrix $J^{[2]}(W^*)$ is

$$\mathcal{J}^{[2]}(W^*) = \begin{bmatrix} -\overline{a} + \beta & -(1-\epsilon)\mu S^* & (1-\epsilon)\mu S^* \\ \beta & -(\overline{a} + \gamma) & \frac{rS^*}{S_{max}} \\ 0 & (1-\epsilon)\mu V^* & -(\beta + \gamma) \end{bmatrix},$$

.
Now we compute $tr(J(W^*)), det(J(W^*)), det(J^{[2]}(W^*))$ respectively. Hence $tr(J(W^*)) = -\overline{a} - \beta - \gamma < 0$,

$$det(J(W^*)) = -\overline{a}[\beta\gamma - (1 - \epsilon\beta\mu S^*)] + \frac{rS^*}{S_{max}}(1-\epsilon)\mu V^*\gamma - (1-\epsilon)^2\mu^3 S^*\beta V^* < 0,$$

$$det(J^{[2]}(W^*)) = -(\overline{a}+\beta)(\overline{a}+\gamma)(\beta+\gamma) - \frac{rS^*}{S_{max}}(1-\epsilon)(\overline{a}+\beta)\mu V^* + (1-\epsilon)\mu S^*\beta[(\beta + \gamma) + (1-\epsilon)\mu V^*] < 0.$$

Hence by Lemma 3, W^* is locally asymptotically stable. □

5 Numerical result and discussion

The numerical solution of the model is performed though various model parameters. All the parameters and their values used for model (3.1) are taken from [1, 19] and presented in Table 5.
Table 5 Parameters used for model (3.1).

Descriptions	Symbols	Values
CD4+ T cell source rate	Λ	0.1 $mm^{-3}day^{-1}$
Natural turnover rate of uninfected CD+T cell	α	0.02 day^{-1}
Natural turnover rate of infected CD4+ T cell	β	0.3 day^{-1}
Natural turnover rate of Virus	γ	2.4 day^{-1}
Average number of virus cells produced	N	10
Drug efficacy	ϵ	0.5
CD4+ T cell infection rate	μ	0.0027 $mm^{-3}day^{-1}$

We have discussed the locally asymptotically stability of both infection free equilibrium W_0 and chronic infection equilibrium W^* above. When $R_0 > 1$, the endemic equilibrium W^* may only be stable for r small or large. Our numerical solutions consistently show the existence of periodic solutions when W^* is unstable. For the numerical result we use the parametric values used in Table 5 taken from [1] and [19] but with the variation of r . Considering $S_{max} = 1500mm{-}3$, we have shown local stability of both the healthy CD4+ T cells and HIV virus at $r = 0.05$ and $r = 3$ (see Figures 4 and 6). Whereas at $r = 0.8$, W^* is unstable and a periodic solution exists (see Figure 5).

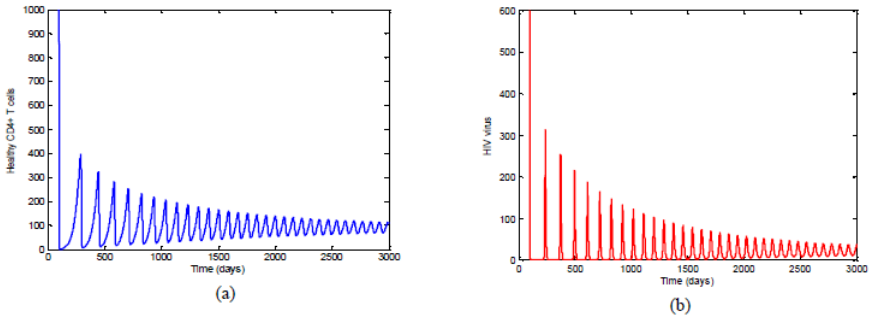

Figure 4: Using the parameter values of Table 1, W^* is is stable, when $r = 0.05$ and $R_0 = 0.5081$.

We observe W^* is unstable within the range of r between 0.093453 and 1.9118. From Figure 5, we observe viral load 600 mm^{-3} persists when $r = 3$ while it is below 100 mm^{-3} at $r = 0.05$. Again when $r = 3$ the initial oscillation disappears after 145+ days whereas at $r = 0.05$ the damped oscillation are clearly visible after 2000 days. We also note that, the values of R_0 in these three cases are 0.5081, 0.8227 and 0.48431 respectively.

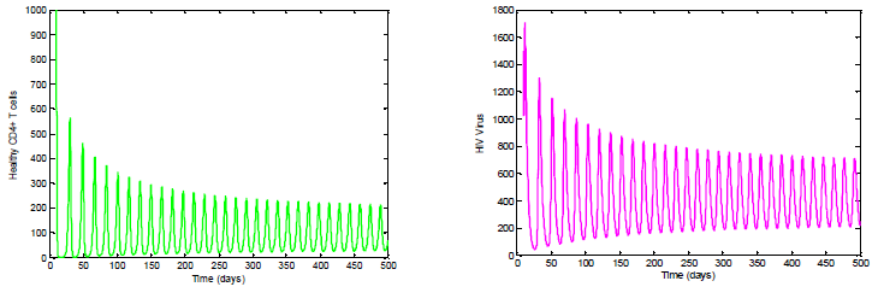

Figure 5: When $r = 0.8$ and $R_0 = 0.8227$, a periodic solution is observed.

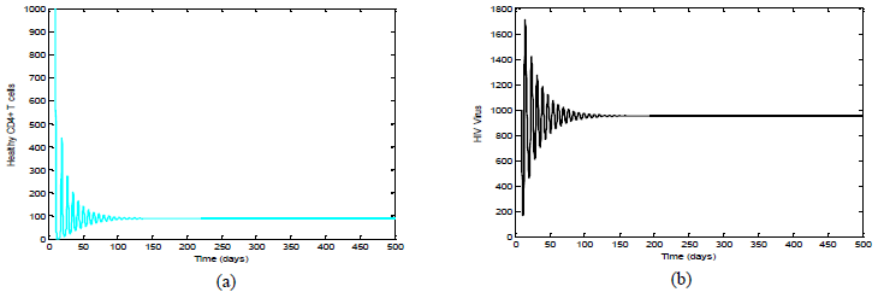

Figure 6: W^* is stable when $r = 3$ and $R_0 = 0.48431$.

Conclusion

The low prevalence rate of HIV infection in Bangladesh have been possible because, several NGOs have played a magnificent role in keeping the HIV prevalence low by enhancing awareness to people. But this low prevalence rate is increasing day by day and becoming a great threat to us. In this paper, we have shown a brief report of HIV/AIDS of Bangladesh from 1989 to 2015 (except 2008). Again we have discussed the mathematical presentation of HIV infection in three compartmental model. In the model, we added a probability term ϵ with the infected T cells. Then we have calculated the basic reproduction number $R_0 = \frac{(1-\epsilon)\mu S_0}{\gamma}$ where, S_0 is considered as equilibrium of CD4+ T cells in the absence of HIV infection. At disease free equilibrium point the model is assumed to stable and later we conclude the stable and unstable condition for the chronic infected equilibrium points. With the proliferation term r and reproduction number we find the solution of it. We find the numerical solution at different equilibrium points and have observed the curve in periodic and damped oscillation.

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