Global Stability Analysis of HIV+ Model

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Abstract. We developed and studied a mathematical model of HIV+. Two equilibriums points were found, disease free and endemic equilibrium, and basic reproduction ratio R_0 was also calculated by the use of next generation matrix. Global stability analysis of the equilibria was carried out by the use of Lyapunov function, and it was shown that the stability of the equilibria depends on the magnitude of the basic reproduction ratio. When $R_0 < 1$, the disease free equilibrium is globally asymptotically stable, and disease dies out. On the other hand if $R_0 \geq 1$, the endemic equilibrium is globally asymptotically stable and epidemics occurs. Reported cases of 13646 HIV-1 positive were obtained in the year 2016 from Ministry of Health, Turkey (MOH). This data is used to present the numerical simulations, which supports the analytic result. R_0 was found to be 1.98998, which is bigger than 1, this shows the threat posed by HIV in Turkey.

Keywords: HIV · AIDS · Mathematical model · Global stability
Basic reproduction ratio · Turkey

1 Introduction

Historically, infectious diseases posed a real threat to the human population. Although they have been in human population all the time to some extent, the effects of epidemics are the most obvious and noticeable. Only in the 14th century Europe, around 25 million out of about 100 million individuals died from the Black Death [1]. Several diseases were discovered in America which included smallpox, measles, influenza, and typhus, whooping cough, the mumps, and diphtheria. Infectious disease was the main reason for the demise of the Indians [2]. In the early 1980's, some homosexual men in the United States were diagnosed with a type of fungal infection and a tumor called Candidiasis and Kaposi's sarcoma respectively. Paris Pasteur institute in 1984 detected a virus responsible for those diseases and called it the Human Immunodeficiency Virus (HIV) [3].

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HIV is the virus that causes Acquired Immunodeficiency Syndrome (AIDS). The virus is responsible for attacking and destroying the immune systems mainly the CD4+ T-lymphocytes or T-cells [1]. On a normal basis, these CD4+ T-lymphocytes or T-cells detect foreign and infected cells, and attack, spread and kill them [1–3]. HIV is able to infect CD4+ T-lymphocytes and insert its genome to host genome. This integrated HIV genome may exist in 2 states. They can be either transcriptionally active generating new viruses that can infect other CD4+ T-lymphocytes or in latent state which may become activated later. In transcriptionally active stage, the infected CD4+ T-lymphocytes die due to cytopathic effect of the virus. As a result, the number of CD4+ T-lymphocytes, which are able to recognize foreign and infected cells, declines, and this decrement lead stoper manent and lasting damage to the immune system [3]. The immune system finally loses its ability to fight and kill infections due to the number of CD4+ T-lymphocytes count which is so small. When an individual reaches this stage, the person is said to have AIDS [4]. The time between getting infected with HIV and advancing to AIDS is, in general, five years but changes due to many factors. If the CD4+ T-lymphocytes cells count falls below 200 cells/mm^3, then the person is considered to be in the "AIDS phase", otherwise the person is said to be HIV infected [5]. The mode of transmission of HIV includes heterosexual intercourse, homosexual/bisexual intercourse, intravenous drug use, vertical transmission, and unknown reasons [6].

Since its discovery (HIV/AIDS), the extensive increase and epidemic continues around the globe. The greatest number in any one year was in 2003, where almost five million individuals became newly infected, with a total of 38 million HIV/AIDS patients, and almost three million people died from AIDS in the same year [7]. To continue its record of one of the most destructive epidemics in history, it killed at least 25 million people by 2005. Efforts to improve the use of antiretroviral treatment in some part of the world were still not enough to reduce a significant number of deaths, the HIV/AIDS epidemic claimed 3.1 million lives in 2005, of which about 570000 were children (UNAIDS/WHO [8]).

The region that suffered most is Africa, with Sub-Saharan Africa as the home of the epidemic. In 2010, 2.7 million people were newly infected, and 1.8 million patients died of AIDS-related causes across the globe. By the end of 2010, around 34 million individuals were victims of HIV/AIDS [9]. China stated that about 2.8 million died of AIDS-related causes in 2011, and there were about 7.8 million HIV-infected individuals by the end of 2011. In the year 1985, two patients were diagnosed with AIDS in Turkey, since then, the importance of AIDS started and still continue to be on the forefront. The number of new cases increases every year, with 34, 91, and 119 cases in 1990, 1995, and 1999 respectively [10].

In 2004, the Ministry of Health (MOH) published the total number of HIV patients 1802, of which 76% are between the ages of 15 to 49 years and sexually active. Among these patients, about 800 were AIDS patients. This is an official data from MOH, however, these numbers does not reflect the actual figures of HIV infected individual in Turkey, due to insufficiency of the registration system, and the lack awareness and phobia of the patients to attend health centers or hospitals [11].

At the end of 2011, the ministry stated that the total number of HIV/AIDS infected people was 5224. It also published in 2013 that at least 6000 individuals were infected with HIV, and the numbers of newly reported cases in 2010, 2011, and first six months of 2013 were 589, 1068, and 587 respectively. According to a report, poor knowledge of sexually transmitted diseases, poor socio-economic conditions, increase in number of unregistered sex workers, increase in number of homosexuals, and intravenous drug use contributed to the spread of HIV infection in Turkey. It was reported that, the main way of transmitting HIV in Turkey is via heterosexual sex (53%), then men having sex with men (MSM at 9%), and intravenous drug users (IDU at 3%) among the recorded cases. According to Positive Living Association Istanbul, personal communication, HIV/AIDS will become a major public health issue in Turkey in the coming years, as such; it must be regarded as a rising disease for Turkey [12].

The main ways in which HIV/AIDS is transmitted between individuals are now well understood, but the factors that contribute to the disparities in its prevalence and trends among populations remain an area of interest to scientific researchers. To understand these disparities, it is essential to understand the system, its components and its dynamics. Mathematical models of HIV/AIDS transmission dynamics are important research tool in this category [13, 14].

Primary purpose of any mathematical model of HIV transmission lies in using individual level inputs to project population level outcomes. Some of the important outcomes that can be examined with a model are; the incidence of infection, the prevalence of infection, or the doubling time of the epidemic. More important than these however, is simply the likelihood of an epidemic to occur that is whether there is sufficient transmission potential for a chain of infection to be sustained. This outcome is termed by a simple summary statistic: the reproduction number of the infectious process, R_0. In a susceptible population, R_0 represents the expected number of secondary infections generated by the first infected individual. If R_0 is equal or greater than 1 an epidemic is expected. If R_0 is less than 1, the infection is expected to die out [15].

The magnitude of R_0 is used to measure the risk of an epidemic or pandemic in any emerging infectious disease. It was used for understanding the outbreak and danger of SARS. R_0 was also used to characterize bovine spongiform encephalitis (BSE), foot and mouth disease (FMD), strains of influenza, and West Nile Virus [16–19]. The incidence and spread of dengue, Ebola, and scrapie have also been assessed by R_0 [20–22]. Tropical issues such as the risks of indoor airborne infection, bioterrorism, and computer viruses also depend on this important parameter [23–26].

In this paper, we shall first introduce the model involving systems of ODE, and then discuss the biological meaning of the parameters involved. We shall study the global stabilities of both disease free and endemic equilibria by the use of Lyapunov function. By the use of real data obtained from Turkey in 2016, we will conduct numerical simulations to support the analytic result.

The organization of the paper is as follows: In Sect. 2, the model is presented and the basic reproduction number is obtained. In Sect. 3, stability of the equilibria are investigated. In Sect. 4, results are obtained by numerical simulations of the real data obtained from Turkey in 2016. Finally Sect. 5 is the discussion and conclusion of the research.

2 Construction of the Model

The system of ordinary differential equations derived is for the whole Turkish population.

2.1 Susceptibles, S(t)

Consider the birth Λ(t) to the susceptible population per unit time. Susceptibles individuals are removed through infection or through natural death. Let μ be the natural death rate for the whole population. The removal rate of susceptible individuals through infection is the number of new HIV infections per unit time. We use this rate in calculating HIV incidence which by definition is the number of new infected persons in a specified period of time divided by the number of uninfected persons that were exposed for this same time.

2.2 HIV Positives, H(t)

Let each susceptible have c contacts per unit time. Assume that a proportion H/N of these contacts are with infectives and at each of these contacts with infectives, a susceptible has a probability b of becoming infected. Let α the incidence rate, then the total probability of one susceptible getting HIV infected from any of their contacts per unit time is αH/N. This is the expression for the force of infection. The force of infection is the probability that a susceptible will get an HIV infection per unit time. Therefore in a population of S susceptibles, the number of new HIV infections per unit time is given by αHS/N. Infectives are recruited through new HIV infections described above and removed through death at rate v and through natural death at rate μ. Hence, 1/v is the duration spent in the infective stage and 1/μ is the life expectancy of the population. All these rates are assumed constant in the model.

2.3 Removed Phase, R(t)

Removed cases are recruited either through natural death μ or through deaths due to HIV at the rate v.

With these assumptions, we arrive at the following system of ODE.

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \frac{\alpha SH}{N} - \mu S \\ \frac{dH}{dt} &= \frac{\alpha SH}{N} - (v+\mu)H \\ \frac{dR}{dt} &= (v+\mu)H + \mu S \end{aligned} \tag{1}$$

$$S(t) > 0, \quad H(t) \geq 0, \quad \textit{and} \quad R(t) \geq 0$$

Since $N = S + H + R$, then Eq. (1) can be reduced to

$$\frac{dS}{dt} = \Lambda - \frac{\alpha SH}{N} - \mu S$$

$$\frac{dH}{dt} = \frac{\alpha SH}{N} - (v+\mu)H \tag{2}$$

It follows from (1) that,

$$[S+H+R]^{|} = \Lambda - \frac{\alpha SH}{N} - \mu S + \frac{\alpha SH}{N} - (v+\mu)H + \mu S + (v+\mu)H \leq \Lambda$$

Then

$$\lim_{t\to\infty} sup(S+H+R) \leq \Lambda$$

Thus the feasible region for (1) is

$$\pi = \{(S+H+R) : S+H+R \leq \Lambda, S(t) > 0, H(t) \geq 0, R(t) \geq 0\}$$

2.4 More Assumptions

For the simulation we make further assumptions as follows;

(i) S(0) is considered to be the whole population in 2016
(ii) We considered homogeneous mixing in the population
(iii) $v = 0.01493$ is considered (That is averagely 67 years is the life span of HIV+ people)

2.5 Equilibrium Points

Equating the equations in (*) to zero and solving simultaneously we find two equilibrium points. Disease free and endemic equilibrium points.

$$E_0 = \left(S_0 = \frac{\Lambda}{\mu}, H_0 = 0\right)$$

and

$$E_1 = \left(S_1 = \frac{v+\mu}{\alpha}, H_1 = \frac{\Lambda\alpha - \mu v - \mu^2}{\alpha(v+\mu)}\right)$$

2.6 Basic Reproduction Ratio

This is the number of secondary infections caused by a single infective individual in a completely susceptible population. It is denoted by R_0. Using the next generation of matrix (NGM) method we have,

$$\begin{array}{cccc} F = [\alpha SH] & & & V = [(v+\mu)H] \\ M = \partial F = [\alpha S] & & & M(E_0) = [\alpha S_0] \\ K = \partial V = [v+\mu], & K^{-1} = \frac{1}{v+\mu}, & & MK^{-1} = \frac{\alpha S_0}{v+\mu}. \end{array}$$

The spectral radius, which is the dominant eigenvalue, is $\frac{\alpha S_0}{v+\mu}$

Hence the basic reproduction ration is;

$$R_0 = \frac{\alpha S_0}{v+\mu}$$

3 Global Stability Analysis of the Equilibria

In this section stability analysis of the two equilibrium points is obtained by the use of Lyapunov function. The conditions for the global stability of the equilibria in each case depends on the magnitude of the basic reproduction ratio R_0. Hence we have the following theorems and their proofs.

Theorem 1: The disease free equilibrium is globally asymptotically stable when $R_0 \leq 1$.

Proof: We construct the following Lyapunov function

$$V = (S - S_0 lnS) + H + C$$

Where $C = S_0 lnS_0 - S_0$

$$\begin{aligned} \dot{V} &= \left(1 - \frac{S_0}{S}\right)\dot{S} + \dot{H} \\ &= \left(1 - \frac{S_0}{S}\right)[\Lambda - \alpha SH - \mu S] + \alpha SH - (v+\mu)H \\ &= \Lambda - \alpha SH - \mu S - \Lambda\frac{S_0}{S} + \alpha S_0 H + \mu S_0 + \alpha SH - (v+\mu)H \\ &= \mu S_0\left(2 - \frac{S}{S_0} - \frac{S_0}{S}\right) - [(v+\mu) - \alpha S_0]H \end{aligned}$$

< 0 by the relation between geometric and arithmetic means and if $\alpha S_0 \leq (v+\mu)$. This implies $\dot{V} \leq 0$ *if* $R_0 \leq 1$.

Theorem 2: The endemic equilibrium E_1 is globally asymptotically stable when $R_0 > 1$.

Proof: We construct the following Lyapunov function

$$V = (S - S_1 lnS) + (H - H_1 lnH) + C$$

Where

$$C = -[S_1 - S_1 lnS_1 + H_1 - H_1 lnH_1]$$

$$\begin{aligned}
\dot{V} &= \left(1 - \frac{S_1}{S}\right)\dot{S} + \left(1 - \frac{H_1}{H}\right)\dot{H} \\
&= \left(1 - \frac{S_1}{S}\right)[\Lambda - \alpha SH - \mu S] + \left(1 - \frac{H_1}{H}\right)[\alpha SH - (v+\mu)H] \\
&= \Lambda - \alpha SH - \mu S - \Lambda\frac{S_1}{S} + \alpha S_1 H + \mu S_1 + \alpha SH - (v+\mu)H - \alpha SH_1 + (v+\mu)H_1 \\
&= \mu S_1\left[2 - \frac{S}{S_1} - \frac{S_1}{S}\right] - \left[(v+\mu) - \alpha\left(\frac{v+\mu}{\alpha}\right)\right]H - [\alpha S - (v+\mu)]\left[\frac{\alpha\Lambda - \mu v - \mu^2}{\alpha(v+\mu)}\right]
\end{aligned}$$

< 0 by the relation between arithmetic and geometric mean and if $\alpha\Lambda - \mu v - \mu^2 > 0$

This implies $\dot{V} \leq 0$ *if* $R_0 > 1$.

4 Results

In this section, results are calculated by simulating the model using the real data obtained from Turkey in 2016.

4.1 HIV in Turkey

Here we use the real data obtained from MOH, in which there were a total of 13646 HIV-1 positive reported cases in the year 2016, in the year 2016 to study and predict the dynamics of HIV in Turkey using our model. Table 1 presents the values of the parameters as calculated based on the data obtained.

4.1.1 Equilibrium Points

$$E_0 = (s_0 = 2.15, h_0 = 0)$$
$$E_1 = (S_1 = 1.0804, H_1 = 1.0676)$$

Table 1. Model parameters as calculated from the data

Parameters	Values
$s = \frac{S(t)}{N(t)}$	0.99992581
$h = \frac{H(t)}{N(t)}$	0.00007419
Λ	17.2
μ	8
A	7.4184
V	0.01493

4.1.2 Basic Reproduction Ratio

$$R_0 = \frac{\alpha S_0}{v + \mu} = 1.98998$$

Since $R_0 > 1$, the disease free equilibrium is not stable and the endemic equilibrium is stable. Hence, there is going to be epidemics.

4.1.3 Numerical Simulation

Simulating the above result, Fig. 1 shows the epidemic of HIV/AIDS in Turkey.

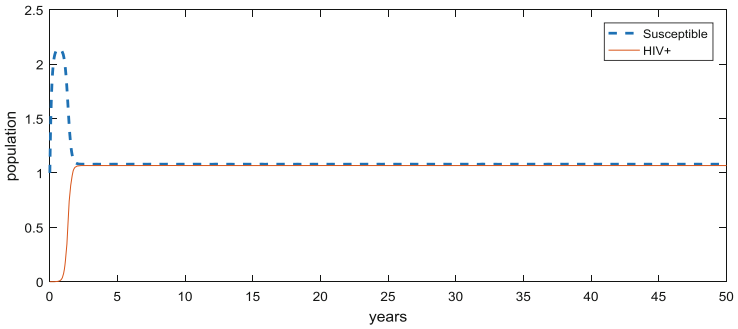

Fig. 1. Dynamics of HIV/AIDS in Turkey

5 Discussion

A mathematical model for HIV+ is constructed and analyzed. Two equilibrium points (disease free and endemic) are found and stability of each of the equilibrium point was shown to depend on the magnitude of basic reproduction ratio, using Lyapunov function. It was shown that if $R_0 = \frac{\alpha S_0}{v + \mu}$ is less than one, the disease free equilibrium is globally asymptotically stable. Also, if the value is greater than or equals to one the endemic equilibrium is globally asymptotically stable.

The Turkish population in the year 2016 is 79814871, and the HIV positive population is 13646. The value of the basic reproduction ratio is 1.98998, which is bigger than one. This implies one HIV positive individual in Turkey can be able to transfer the disease to almost 2 individuals, hence there is going to be HIV epidemic in Turkey.

Numerical simulations were carried out and the results support the analytic findings. The results in the simulation shows that if appropriate measures are not taken, in 50 years to come, there will be more HIV positive individuals in Turkey as there are susceptible individuals.

The main limitation to our analysis may be that we did not account for the effect of behavioral change arising both from number of HIV cases in the community as well as awareness by governmental and nongovernmental organizations. Secondary, the possible effects of extensive use of antiretroviral drugs (ARVs) in terms of method of distributing drugs through public or private health institution or a combination of both could determine whether patients on ARVs revert back to the infective class. This together with reduced infectiousness due to lower viral loads for those on treatment was not accounted for.

Despite the limitations mentioned above, there are several implications of our findings to public health. First, the endemic equilibrium should be brought as low as possible especially during the first wave of the epidemic. This model suggests that this can be achieved by prolonging the lifetime of the HIV patients for as long as possible. Second, HIV prevalence at low prevalence levels become less sensitive to changes in the dynamics of HIV epidemic because it is overpowered by demographic changes especially the recruitment of susceptibles. At low prevalence levels, there is hence need to track trends in number of persons infected with HIV than tracking HIV prevalence.

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