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HIV/AIDS Mathematical Model Based on Virus Load and Effectiveness in ART Treatment.

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Abstract

HIV/AIDS treatment exists to keep the viral load at an undetectable level to prevent the transmission of its virus. The antiretroviral therapy (ART) allows an extended life span for a treated person, keeping the viral load under control, even for patients who had low adherence to the treatment and return to take it in the appropriate way. In this sense, our work take as a main hypotheses the effectiveness of ART treatment. The aim of this work is to represent the HIV/AIDS population dynamics using a deterministic mathematical model of non linear ordinary differential equations. We specifically study sexual, injectable drug users and vertical transmission. We present a model considering viral load as the main characteristic to determine the different stages of the infection. The mathematical model is presented, the basic reproduction number is analyzed and some numerical simulations were made.

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1 Introduction

Human immunodeficiency virus (HIV) and subsequent Acquired Immunodeficiency syndrome (AIDS) is one of the main health problems in the world. The HIV virus weakens the person's immune system, exposing it to any opportunistic disease. According to UNAIDS in 2017, 36.9 million people were infected with HIV worldwide, 21.7 million people have had access to treatment with antiretrovirals (ART) and 9.4 million people did not know they were living with the virus. This disease has claimed the lives of 35.4 million people for AIDS-related causes [12].

HIV is transmitted sexually by contact with infected body fluids such as blood, semen, vaginal or rectal fluids; vertically from an infected mother to a child during pregnancy, birth or lactation; by injectable drug users sharing needles with infected blood and by blood transfusion [3]. Several measures have been used to control the spread of the virus, such as educational campaigns about the use of condoms, voluntary HIV testing, access to sterile syringes for drug users and antiretroviral therapy for infected and exposed people. Nevertheless, the antiretroviral therapy has proven to be the most effective and used because, in addition to extending the life of the infected patient by delaying the onset of symptoms, it keeps the viral load at undetectable levels, making it possible to have a normal sexual life [10].

The present research shows the dynamics in a population exposed to contagion, considering different viral loads whether or not enrolled in an ART treatment. According to the objective for HIV proposed by UNAIDS [11], 90% of the treated people have an undetectable viral load, in this way, 10% don't take the allocated drugs or the HIV virus is resistant to the treatment. Life expectancy for people living with HIV enrolled in an antiretroviral therapy with good adherence to treatment, and consequently with undetectable viral load, is better than that of people with a detectable viral load [2, 10].

This work is organized as follows; in section 2 we shows some preliminaries to model the HIV infection, in section 3 the assumed hypotheses in the dynamic's disease are presented, in section 4 the mathematical model is presented, in section 5 the basic reproduction number is analyzed and some numerical simulations are shown. Finally, our work ends with a conclusion in section 6.

2 Preliminaries

The chosen model consider three forms of virus transmission: due to sexual relations, vertical transmission and injectable drugs transmission. Infected people are defined as those with high viral load, this means more than 100,000 copies of HIV RNA in a millilitre of blood, [2], they will be considered undiagnosed or untreated. On the other hand, the treated population with low adherence to the ART treatment, generally has a detectable viral load. The undiagnosed infected individuals or detectable persons are responsible for the HIV virus transmission, because they do not take the treatment correctly. However, a great part of the treated population has a good adherence to the treatment. In this sense, if they have this good adherence this implies in a good immunological response, which, in turn, implies that their viral load is undetectable. It is important to highlight that people with AIDS and good adherence to the treatment do not participate in the chain of infection, because their viral load is undetectable and consequently the transmission is negligible.

3 Dynamic and assumed hypotheses

- Recruitment is due to constant entry of susceptible individuals and susceptible newborn of treated undetectable and detectable populations.
- Once a susceptible is infected, it has three possible new stages; undetectable treated, detectable treated with antiretroviral therapy or untreated.
- Persons who don't know they are infected or are not enrolled in antiretroviral therapy are defined as untreated. When symptoms of AIDS are shown, we assumed that the person will be diagnosed and enrolled in ART therapy, in this way they can be among those living with AIDS with undetectable viral load.
- An undetectable treated person can develop AIDS keeping their undetectable state. Also, it is possible for an undetectable treated person with symptoms, to return to be an asymptomatic, it is not considered that an undetectable viral load becomes detectable.
- The natural mortality rate is the same in all classes, the induced mortality in people living with AIDS (with undetectable viral load) is assumed less than the induced mortality rate in people living with AIDS with detectable viral load. In fact, the first induced mortality is the fourth part of the induced mortality in detectable individuals.

4 Mathematical model

This model considers 6 disjoint classes: $S(t)$ susceptible people who can be infected, $I(t)$ infected people who can infect others, $T_d(t)$ treated people with detectable viral load and poor adherence to treatment, $T_u(t)$ treated people with undetectable viral load, $A_u(t)$ people treated living with AIDS with undetectable viral load and $A_d(t)$ people living with AIDS with detectable viral load. $D(t)$ means the population with detectable viral load given by $D(t) = I(t) + T_d(t) + A_d(t)$, and the total population given by $N(t) = S(t) + I(t) + T_d(t) + T_u(t) + A_u(t) + A_d(t)$.

The constant recruitment in the susceptible population will be denoted by Ψ, the growth rate is represented by η, the neonate infected proportion is v, $0 \leq v \leq 1$, in this way $v\eta D$ represents the entry of infected newborns from infected individuals with detectable viral load. The transfer-rate from infected to others phases is denoted by α, the proportion of treated people is p, and, consequently, $(1-p)$ denotes the proportion of untreated infected. The proportion of people with good adherence to ART treatment is denoted by τ, the transfer rate to develop AIDS with undetectable viral load is denoted by δ_u, and the transfer rate to develop AIDS with detectable viral load is δ_d. The treatment effectiveness for individuals living with AIDS with undetectable viral load is denoted by b, the natural mortality rate is represented by μ according the references [2, 10] and, the induced mortality rate in people living with AIDS is d, finally, the transfer rate from people living with AIDS from detectable viral load to undetectable viral load is γ. The infection forces are two, due to sexual and by injectable drug users transmission, they depends upon the detectable population and they are given by

$$\lambda_s = \beta_s c_s \frac{I + T_d + A_d}{N} \qquad \text{by sexual transmission, and}$$
$$\lambda_n = \beta_n c_n \frac{I + T_d + A_d}{N} \qquad \text{by injectable drug users.}$$

To reduce notation, the general force of the infection is given by

$$\lambda = \lambda_s + \lambda_n = \beta \frac{I + T_d + A_d}{N} \qquad \text{with} \qquad \beta = \beta_s c_s + \beta_n c_n$$

here $\beta_{s,n}$ represents the probability of transmission by sexual contact or sharing needles respectively, $c_{s,n}$ means rate for sexual partners or sharing needles respectively. In tables 1 and 2 the variables and parameters for the model are listed.

Variables	Description
$S(t)$	Susceptible population
$I(t)$	Infected population with detectable viral load
$T_d(t)$	Treated with detectable viral load
$T_u(t)$	Treated with undetectable viral load
$A_u(t)$	People living with AIDS with undetectable viral load
$A_d(t)$	People living with AIDS with detectable viral load
$N(t)$	Total population

Table 1: Variables

Parameters	Description
Ψ	Recruitment (ind/y)
η	Growth rate (y^{-1})
v	Neonate infected proportion
b	Rate of effectiveness ART treatment in people living with AIDS
μ	Natural mortality rate (y^{-1})
γ	Transfer rate from A_d to A_u (y^{-1})
d	Induced disease mortality rate in A_d (y^{-1})
τ	Proportion of people with good adherence to treatment
p	Proportion of treated people
α	Progression rate out of Infected (y^{-1})
$\delta_{u,d}$	Transference rate to develop AIDS with undetectable viral load (y^{-1})
$\beta_{s,n}$	Transmission probability by sexual contact or sharing needle
$c_{s,n}$	Rate for sexual partners or sharing needle (y^{-1})

Table 2: Parameters

The compartmental diagram is show in figure 1

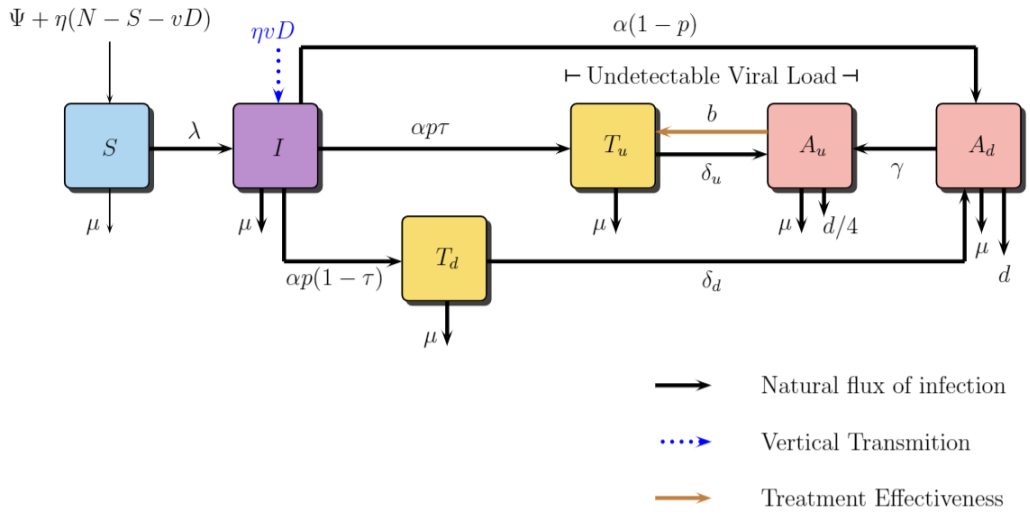

Figure 1: Diagram

The dynamic is governed by the following non linear ordinary differential equation system (1).

$$\begin{aligned}
\frac{dS}{dt} &= \Psi + \eta(T_u + A_u) + \eta(1-v)(I + T_d + A_d) - (\lambda + \mu)S \\
\frac{dI}{dt} &= v\eta(I + T_d + A_d) + \lambda S - (\alpha + \mu)I \\
\frac{dT_u}{dt} &= \alpha p\tau I + bA_u - (\delta_u + \mu)T_u \\
\frac{dT_d}{dt} &= \alpha p(1-\tau)I - (\delta_d + \mu)T_d \\
\frac{dA_u}{dt} &= \delta_u T_u + \gamma A_d - \left(b + \mu + \frac{d}{4}\right)A_u, \\
\frac{dA_d}{dt} &= \delta_d T_d + \alpha(1-p)I - (\gamma + \mu + d)A_d
\end{aligned} \tag{1}$$

5 Results

5.1 Basic Reproduction number R_o

The basic reproduction number R_o is the most important number in epidemiological mathematics, because it represents the average of secondary cases produced by an infected individual during his entire life, the infectious period, when introduced into the susceptible population. This metric is used to determine whether or not an infectious disease becomes an epidemic. When $R_o < 1$ the infection will die out by itself, but if $R_0 > 1$ the infection will be increase and become epidemic. It was obtained according the next generation method using the methodology of Watmough [15], as follows;

Let $x = (I, T_u, T_d, A_u, A_d)$ be the vector of infected populations (detectables or undetectables), and $\mathcal{F}_\rangle$ the vector with new infections in the compartment i, and $\mathcal{V}_\rangle$ the transfer vector and regarding terms. Thus, if $\dot{x}$ denotes the aforementioned system without susceptibles, then $\dot{x} = \mathcal{F} - \mathcal{V}$, where

$\mathcal{F}$ and $\mathcal{V}$ are given explicitly by

$$\mathcal{F} = \begin{pmatrix} \beta\frac{I+T_d+A_d}{N}S \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \qquad \mathcal{V} = \begin{pmatrix} (\alpha+\mu)I - v\eta(I+T_d+A_d) \\ (\delta_u+\mu)T_u - \alpha p\tau I - bA_u \\ (\delta_d+\mu)T_d - \alpha p(1-\tau)I \\ (b+\mu+\frac{d}{4})A_u - \delta_u T_u - \gamma A_d \\ (\gamma+\mu+d)A_d - \delta_d T_d - \alpha(1-p)I \end{pmatrix}.$$

The corresponding Jacobian matrices for $\mathcal{F}$ and $\mathcal{V}$ evaluated in the disease free equilibrium point $E^0 = (\frac{\Psi}{\mu}, 0, 0, 0, 0)$, are given by

$$F = \begin{pmatrix} \beta & 0 & \beta & 0 & \beta \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} a_1 & 0 & -v\eta & 0 & -v\eta \\ -\alpha p\tau & a_2 & 0 & -b & 0 \\ -\alpha p(1-\tau) & 0 & a_3 & 0 & 0 \\ 0 & -\delta_u & 0 & a_4 & -\gamma \\ -\alpha(1-p) & 0 & -\delta_d & 0 & a_5 \end{pmatrix},$$

where $a_1 = \alpha + \mu - v\eta, \quad a_2 = \delta_u + \mu, \quad a_3 = \delta_d + \mu, \quad a_4 = b + \mu + \frac{d}{4}, \quad a_5 = \gamma + \mu + d.$
Finally, the basic reproduction number defined as the spectral radius of the matrix FV^{-1} is denoted by

$$R_0 = \frac{\beta\Big[a_3\big(a_5 + \alpha(1-p)\big) + \alpha p(1-\tau)\,(a_5+\delta_d)\Big]}{a_3\Big[a_1a_5 - \alpha\eta v(1-p)\Big] - \alpha\eta v p(1-\tau)\,(a_5+\delta_d)} \tag{2}$$

5.2 Numerical Simulations

We have conducted numerical experiments using a fourth-order Runge Kutta method to solve system (1). In order to observe the dynamical behavior, we assumed the following initial conditions $S(0) = 0.99,\ I(0) = 0.1,\ T_u(0) = 0,\ T_d(0) = 0,\ A_u(0) = 0,\ A_d(0) = 0$ and the chosen parameters are showed in the table 3.

Parameters	Value		Source	Parameters	Value		Source
Ψ	0.0345	ind/y	[8]	β_s	0.0200		[14]
η	0.0150	y^{-1}	[5]	c_s	2	y^{-1}	[1]
v	0.2000		[6]	γ	0.0200	y^{-1}	Assumed
b	0.3300	y^{-1}	[7]	τ	0.9500		Assumed
μ	0.0149	y^{-1}	[13]	δ_u	0.0330	y^{-1}	Assumed
d	0.2000	y^{-1}	[9]	δ_d	0.0200	y^{-1}	Assumed
p	0.7500		[4]	β_n	0.1000		Assumed
α	0.0740	y^{-1}	[1]	c_n	2	y^{-1}	Assumed

Table 3: Values of the parameters for the numerical simulations.

Figure 2 represents the dynamical behavior of the populations for the chosen parameter group and initial conditions. Moreover, the correspondent basic reproduction number using this parameters is $R_0 = 3.27393$.

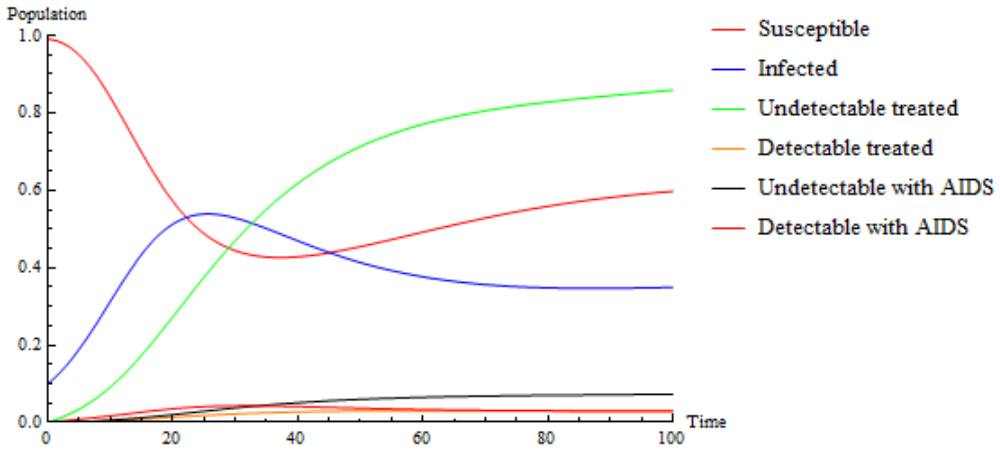

Figure 2: Populations behaviour.

Numerically exploring different parameter configurations and comparing with the obtained R_0 in (2), we find that β_n and c_n are a very sensitive parameters. Let us numerically analyze the basic reproduction number in function of the injectable drug users transmission. Figure 3 shows the plot of $R_0(c_n, \beta_n)$ and the plane $z = 1$. Under the plane $z = 1$ the infection is not considered epidemic. Furthermore, figure 4 shows the region of non-epidemic as a function of drug users c_n and, the range of c_n is assumed to be in the interval $[0, 4]$ (per year) and Infection Probability by sharing needle; β_n is $[0.02, 0.2]$ (non dimensional). It can be seen that increasing the injectable drug user rate from $c_n = 0$ to $c_n = 1.66532$, the probability infection for sharing needles, β_n, must be small, into the region of figure 4, to keep $R_o < 1$ and consequently, not to have an epidemic. On the other hand, if the probability infection increases from $\beta_n = 0.02$ to $\beta_n = 0.2$, the rate of injectable drug users c_n must be small, into the region, but in comparison with aforementioned case, its dependence is less important because if β_n is in the interval $[0.02, 0.2]$ and $0 \leq c_n \leq 0.166532.2$, the basic reproduction number is always less than one.

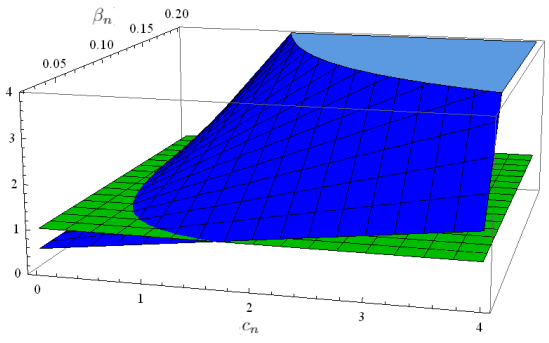

Figure 3: Plot of R_0.

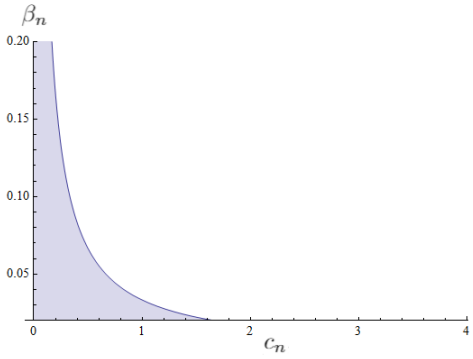

Figure 4: Non epidemic region.

6 Conclusions

Our contribution is to define a model based on the virus quantity to establish the difference between populations, particularly, by giving importance to the detectability and efectiveness of the ART

treatment. For this purpose, we have constructed a model which represents a general behavior of the HIV infection of injectable drugs, sexual and vertical transmissions. Thus, given system (1) and subsequently, the process to perform figure 2, it is possible to conclude that β_n, c_n become essential for the dynamics. In fact, the basic reproduction number is directly proportional to these parameters, see equation (2). Therefore, in subsection 5.2, an analysis of the basic reproduction number showed that fixing all the others parameters, the non-epidemic region is smaller than the epidemic region, concluding that parameter β_n (infection probability in injectable drug transmission) is less sensitive than c_n (rate of drug users sharing needle).

7 Thanks

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