MATHEMATICAL SIMULATION OF HIV/AIDS TRANSMISSION DYNAMICS INCORPORATING DRUGS RESISTANT COMPARTMENT

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Abstract
HIV/AIDS has continued to pose threat to human race globally ensuing death of millions every year all over the world despite countless research works and availability of anti-retroviral drugs as means of combating the virus. This research formulated a mathematical model to study the spread dynamics of HIV/AIDS in the presence of Highly Effective Antiretroviral Treatment (HART) incorporating HART resistance compartment. The basic reproduction number was obtained using the next generation matrix method. The analytical solution of the model was obtained using homotopy perturbation method and the simulations were carried out using MAPLE 18 software. The result shows that drug resistance have significant effect on the AIDS compartment while treatment and condom usage have effect on the total infected populations

Keywords: Basic Reproduction Number, Disease Free and Endemic Equilibria, Homotopy Perturbation, Locally and Globally Assymptotically Stable, Simulation.

Introduction

Human Immunodeficiency Virus (HIV) is an infection which terminates the body resistant systems, increases the risk of certain pathologies, harms body organs such as the brain, kidney, heart and causes death. AIDS which is the late stage of untreated HIV is one of the leading epidemics in the world. As at 2016, about 36.7 million people were living with HIV/AIDS globally, out of which only 20.9 million people were having access to the antiretroviral treatment. 1.18 million people became newly infected. Totally, about 78 million people have been infected with HIV since the discovery of epidemics and about 35 million people died from HIV/AIDS related cases. Recently known infected persons globally numbers at 2.1 million. In Nigeria, about 3.5 million persons are reported to be carrying the deadly virus. According to the United Nations Programme on HIV/AIDS (UNAIDS)(2016), mortality tolls at 180000 individuals both old and young, with a prevalent rate of 3.1% among adults aged 15 and above (UNAIDS, 2016). The United Nations International Children's Emergency Fund (UNICEF)(2004) stated that, HIV/AIDS can be contracted through unprotected sex with an infected person, breast milk of an infected woman, blood transfusion from an infected person and sharing of sharp objects with infected persons.

Although HIV/AIDS is not yet curable, there are antiretroviral drugs that help in boosting the immune system against cell infections. These antiretroviral drugs are categorized into two groups which are Reverse Transcriptase Inhibitors (RTIs) and Protease Inhibitors (PIs). RTIs disrupts the conversion of RNA of the virus to DNA so that new HIV infection of cells is prevented. On the other hand, PIs hinders the production of the virus particles by the actively infected $CD4^+$ T cells (Karrakchou *et al.*, 2006). Mathematical modelling of virus-related infections has resulted to superior indulgent of virus dynamics and helped in suggesting and curbing the spread of viral diseases such as HIV, Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), and Dengue Fever to a minimal level. Amongst the earliest models of HIV infection branded as the basic model was used by (Nowak & May, 2000) and (Perelson & Nelson 1996) and was efficacious in mathematically imitating the dynamics of the early phases of HIV and its objective CD4+ cells resulting in an infection occurrence. Current works have concentrated on HIV viral and cellular infections integrating dynamics such as intracellular delays, latent infection and viral mutation, and spatial heterogeneity (Chen, *etal.*, 2016). For example, (Pourbashash, *et al.*, 2015) investigated the global stability of within host virus models with cell-to-cell viral transmission and achieved a comprehensive analytic explanation of equilibria.

The HIV drug resistance occurs when microevolution causes virions to become tolerant to antiretroviral treatments. These newly created resistant strains of HIV pose a public health issue as they infect a growing number of people because they are harder to treat, and can be spread to other individuals. Microevolution

refers to change in gene frequency within a population "viriological failure" (e.g the frequency of a gene for pesticide resistance in a population can increase between one generation and the next). Although extensive research on HIV transmission dynamics has been carried out, mathematical modelling of HIV incorporating the effect of resistance strain to treatment still remains an area of active research among mathematicians and biologists. Mathematical models have been considered to assess the effect of public sensitization programs (Grace *et al.*, 2017), the use of anti-retroviral drugs and provision of long-time predictions regarding HIV/AIDS prevalence and control in various regions will make a significant impact in combating the disease. This killer virus still lingers in developing countries and remains an important global health challenge. The formulation of a model which captures some essential dynamics of human immunodeficiency virus with public health educational campaign, antiretroviral drugs, and other treatments as control strategies in limiting the effect of the virus with the replication numbers using control measures, were computed and compared with each other to access the possible municipal benefits in this research.

Nosova and Alexei (2013) developed and studied the distribution model of the human immunity deficiency virus (HIV) that includes dynamics in the information of risk groups due to the rise in HIV cases in Russia. In their work, they proposed a model of virus transmission in a population with a dynamic risk due to alcoholism. Their models comprises of eight compartments namely: Socially adapted receptive group S_α, Increased risk of addiction receptive group S_β, Chronic alcoholism receptive group S_A, Drug addiction receptive group S_D, Socially adapted infected group I_α, Increased risk of addiction infected group I_β, Chronic alcoholism infected group I_A and Drug addiction receptive group I_D. The result shows that there is need to take into consideration the social processes in the description of the epidemiology of such infections as HIV. Tentative research propose that co-infection may be accountable for upsurges seen in set-point viral load (spVL) at the within-host level over time (Modjarrad & Vermund, 2010).

These increases due to co-infection (Kublin et al., 2005). Also, the concentrations of co-infection in high-risk groups versus low-risk groups may affect how HIV spreads in the general population (Abu-Raddad et al., 2008). To study the tools responsible for these effects of co-infection, an immune epidemiological model was developed (Cuadros & Ramos, 2012). They found that populations with higher spVL lead to higher increases in viral load due to co-infection, whereas populations with lower spVL leads to lower increases in viral load due to co-infection. This leads to a greater chance of co-infection increasing the occurrence of HIV in populations with high average spVL (Cuadros & Ramos, 2012). Therefore, the effects of co-infection may be alleviated by detecting the viral factors that can shrink the spVL in the population.

The HIV immune epidemiological models combine the immune-viral dynamics at the within-host immunological scale with the transmission dynamics at the between-host epidemiological scale to analyze HIV dynamics of a single strain infection, co-infection, super-infection, evolution, drug resistance, and treatment protocols in heterogeneous populations.

Saenz and Bonhoeffer (2013) developed HIV transmission dynamics between drug-sensitive and drug-resistant infected individuals. Their model consisted of six compartments namely: susceptible population S, Number of individuals infected with drug-resistant strain and do not receive treatment I_{DRO}, Number of individuals infected with drug-resistant strain and receive treatment I_{DRT}, Number of individuals infected with drug-sensitive strain and do not receive treatment I_{DSO}, Number of individuals infected with drug-sensitive strain and receive treatment I_{DST}, and Number of individuals infected with drug-sensitive strain, receive treatment, and develop resistance I_{DSTr}. Their result shows that HIV immune epidemiological models simulate viral immune dynamics at the within-host scale and the epidemiological transmission dynamics at the between-host scale. They account for longitudinal changes in the immune viral dynamics of HIV positive individuals, and their corresponding impact on the spread in the population.

In the context of HIV evolution, while the transmission rate varies through time depending on the viral load, (Doekes *et al.*, 2017) formulated a model to distinguish between different strains. The transmission rate depends on a predefined infectivity profile which changes depending on the stage of infection, and the frequency of the different viral strains in an infected population. They made the transmission rate depend on the frequency of viral strains that were only in actively infected Cd4+ T cells. Their result shows that

the presence of a latent reservoir can severely delay within-host evolutionary dynamics. This delay increases with the relative size of the reservoir and the rate at which latently infected cells proliferate. Hence after nesting the within-host model into an epidemiological model of population dynamics it was observed that the presence of latent reservoirs can also influence the population-level evolution of the virus.

Egbetade and Ibrahim (2012) researched on the stability analysis for a two-sex mathematical model of HIV where they were interested in the mathematical analysis of the equilibrium points of their model equations. They also formulated theorems based on the basic reproduction number R_0. They found out in their result that virus infection is temporal, and can be cleared if $R_0<1$ and other measures such as improved HIV vaccines, ART, and awareness programs are intensified simultaneously to control the transmission rate of the infection. Hence this research lauds all those who have researched on HIV/AIDS model and extends their works by bridging one of the gaps they left, by introducing drug resistance class into the model.

Model Formulation

Following Saenz and Bonhoeffer (2013), the total human population is divided into five compartments; Susceptible individuals(S), Infectious individuals who are not receiving HART(I_1), infectious individuals who receives treatment but are HART resistant(I_2), infectious individual who receives treatment and are HART non-resistant(I_3) and individuals who are down with AIDS compartment(A).

In formulating our model, the following assumptions were made:

I. It is assumed that every human who are sexually active coming into the population are susceptible to HIV.

ii. A person can only get HIV through unprotected sex with HIV infected human.

iii. Only three HIV infected classes are capable of spreading the virus within the population: Infectious individuals(I_1), infectious individuals who receives treatment but are HART resistant(I_2), infectious individuals who receives treatment and are HART non-resistant(I_3). AIDS(A) individuals are too weak to have sex, hence cannot transmit the virus.

The model schematic diagram is as shown in figure 1:

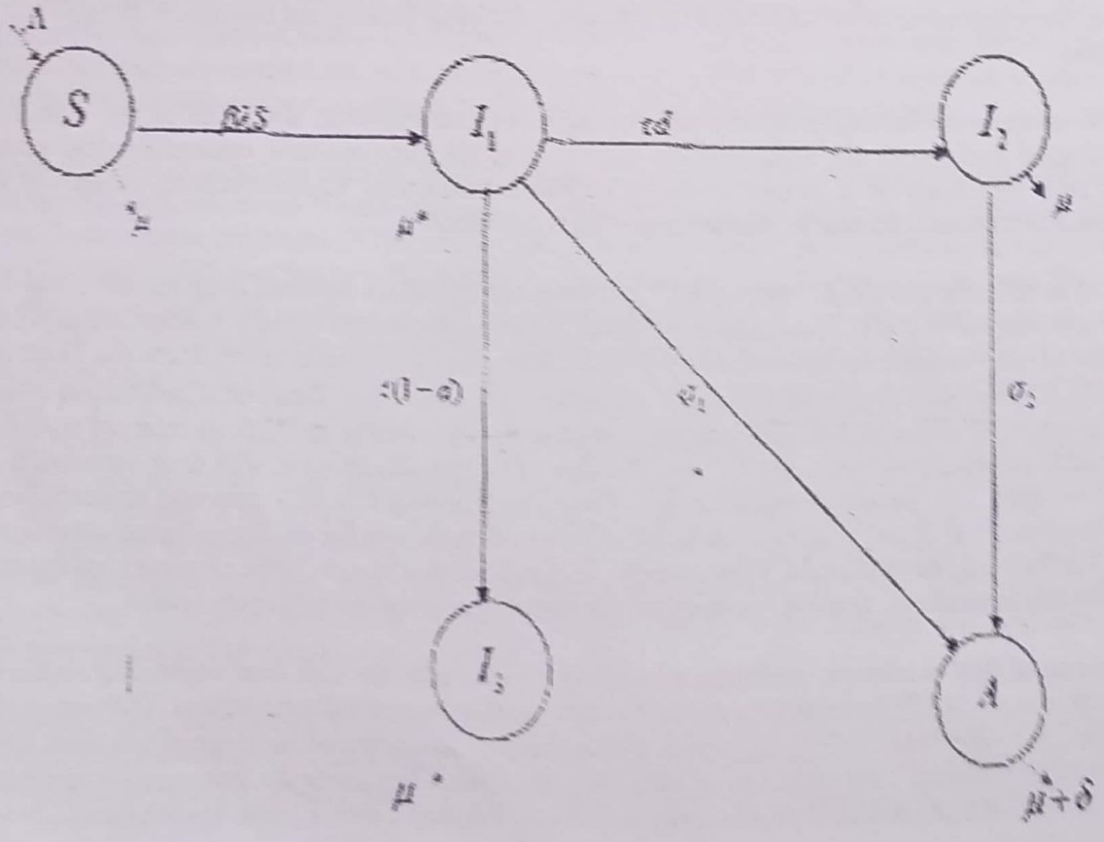

Figure1: Schematic Diagram of HIV/AIDS Transmission Dynamics with Drug Resistance Compartment

The susceptible individuals (S) are generated through constant recruitment of sexually active individuals by immigration at the rate Λ, decreases due to effective contact with I_1, I_2 and I_3 given by the infection force

$$\lambda = \frac{\beta(1-\varepsilon c)[(I_1+I_2)+\eta I_3]}{N} \quad (1)$$

where β is the effective contact rate, ε is the efficacy of HART, c is the compliance level to HART usage and η is the modification parameter associated with reduced infectiousness of I_3 individuals compared to I_1 and I_2. The compartment further decreases due to natural death at the rate μ.

The infectious individuals who are not receiving treatment I_1 are generated through effective contact between S, I_1, I_2 and I_3 as earlier explained. They decrease when they started receiving treatment, or due to progression to AIDS at the rate τ and σ_1 respectively. They further decrease due to natural mortality at the rate μ.

The HART resistant population I_2 are generated when the infectious class I_1 started receiving treatment at the rate τ, but certain individuals in the compartment are resistant to the HART at the rate d. they decreases due to progression to AIDS at the rate σ_2 and further decreases due to natral mortality.

The HART non-resistant population I_3 is generated when the infectious class I_1 is treated at the rate τ as earlier mentioned and they are not resistant to the treatment at the rate (1-d). They only decrease due to natural death.

The AIDS population A is generated from the progression of non-treated infectious individuals and HART resistant individuals at the rate σ_1 and σ_2 respectively. They are reduced due to natural death or disease induced death at a rate

The model equations are as shown:

$$\frac{dS}{dt} = \Lambda - \frac{\beta(1-\varepsilon c)[I_1+\eta(I_2+I_3)]S}{N} - \mu S \quad (2)$$

$$\frac{dI_1}{dt} = \frac{\beta(1-\varepsilon c)[I_1+\eta(I_2+I_3)]S}{N} - (\tau+\sigma_1+\mu)I_1 \quad (3)$$

$$\frac{dI_2}{dt} = (\tau+\phi)dI_1 - (\sigma_2+\mu)I_2 \quad (4)$$

$$\frac{dI_3}{dt} = (\tau+\phi)(1-d)I_1 - \mu I_3 \quad (5)$$

$$\frac{dA}{dt} = \sigma_1 I_1 + \sigma_2 I_2 - (\mu+\delta)A \quad (6)$$

Where

$$N = S + I_1 + I_2 + I_3 + A \quad (7)$$

So that

$$\frac{dN}{dt} = \Lambda - \mu N - \delta A \quad (8)$$

Since the model is dealing with populations, all the variables and parameters of the model are positive with the natural death rates positive, i.e. $(\mu > 0)$, thus considering the region Ω where:

$$\Omega = \{(S, I_1, I_2, I_3, A) \in \Re^5 : S, I_1, I_2, I_3, A \geq 0,\} \quad (9)$$

It can be established that all solutions of the system starting in Ω remain in Ω for all $t>0$. In this region, the usual existence, uniqueness and continuation of results hold for the system.

Equilibrium Points of the Model

Equilibrium state is the point at which there is no external influence on the system. Thus, at equilibrium

$$\frac{dS}{dt} = \frac{dI_1}{dt} = \frac{dI_2}{dt} = \frac{dI_3}{dt} = \frac{dA}{dt} = 0 \quad (10)$$

Let

$$(S, I_1, I_2, I_3, A) = (S^*, I_1^*, I_2^*, I_3^*, A^*, N^*, \lambda^*) \quad (11)$$

At any arbitrary equilibrium point.Thus, the model equations become;

$$\Lambda - \lambda^* S^* - \mu S^* = 0 \quad (12)$$

$$\lambda^* S^* - K_1 I_1^* = 0 \quad (13)$$

$$\tau d I_1^* - K_2 I_2^* = 0 \quad (14)$$

$$\tau(1-d) I_1^* - \mu I_3^* = 0 \quad (15)$$

$$\sigma_1 I_1^* + \sigma_2 I_2^* - K_3 A^* = 0 \quad (16)$$

$$\Lambda - \mu N^* - \delta A^* = 0 \quad (17)$$

where

$$K_1 = (\tau + \sigma_1 + \mu), K_2 = (\sigma_2 + \mu), K_3 = (\mu + \delta) \quad (18)$$

$$\lambda^* = 0 \quad (19)$$

or

$$\left\{ \begin{matrix} (K_1 K_2 K_3 (\mu + \lambda^*) - \delta(K_2 \sigma_1 + \sigma_2 \tau d)\lambda^*) - \\ (\beta(1-\varepsilon c) K_3 (\mu K_2 + \mu \tau d + K_2 \eta \tau (1-d) \end{matrix} \right\} = 0 \quad (20)$$

Disease Free Equilibrium (DFE) Point of the Model

DFE is the state at which the population is free from infections.

Lemma 1: The Disease-Free Equilibrium of the model exists and is given by;

$$(S^0, I_1^0, I_2^0, I_3^0, A^0) = (\frac{\Lambda}{\mu}, 0, 0, 0, 0)$$

Thus, let

$$E^0 = (S, I_1, I_2, I_3, A) = (S^0, I_1^0, I_2^0, I_3^0, A^0) \quad (21)$$

$$(S^0, I_1^0, I_2^0, I_3^0, A^0) = (\frac{\Lambda}{\mu}, 0, 0, 0, 0) \quad (22)$$

Basic Reproduction Number, R_0

The basic reproduction number is the average number of secondary infections caused by a single infectious individual during his/her entire infectious life time. Applying next generation matrix operator to compute the Basic Reproduction Number of the model as used by (Diekmann *et a*, 1990) and improved by (van den Driessche and Watmough 2002). The basic reproduction number is obtained by dividing the whole population into n compartments in which there are $m < n$ infected compartments. Let $x_i, i = 1, 2, 3, ..., m$ be the number of infected individuals in the i^{th} infected compartment at time t. The largest eigenvalue or spectra radius of FV^{-1} is the basic reproduction number of the model.

$$FV^{-1} = \left[\frac{\partial F_i(E^0)}{\partial x_i}\right]\left[\frac{\partial V_i(E^0)}{\partial x_i}\right]^{-1}$$

(23)Where F_i is the rate of appearance of new infection in compartment i to another and E^0 is the disease-Free Equilibrium.

$$F = \begin{pmatrix} \beta(1-\varepsilon c) & \beta(1-\varepsilon c) & \beta(1-\varepsilon c)\eta & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

(24)

$$V = \begin{pmatrix} K_1 & 0 & 0 & 0 \\ -\tau d & K_2 & 0 & 0 \\ -\tau(1-d) & 0 & \mu & 0 \\ -\sigma_1 & -\sigma_2 & 0 & K_3 \end{pmatrix} \quad (25)$$

$$FV^{-1} = \begin{pmatrix} \frac{\beta(1-\varepsilon c)[\mu K_2 + \tau d\mu + \tau\eta K_2(1-d)]}{\mu K_1 K_2} & \frac{\beta(1-\varepsilon c)}{K_2} & \frac{\beta(1-\varepsilon c)\eta}{\mu} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \quad (26)$$

$$\left|fv^{-1} - \lambda I\right| = 0 \quad (27)$$

$$[FV^{-1} - \lambda I] = \begin{pmatrix} \frac{\beta(1-\varepsilon c)[\mu K_2 + \tau d\mu + \tau\eta K_2(1-d)]}{\mu K_1 K_2} - \lambda & \frac{\beta(1-\varepsilon c)}{K_2} & \frac{\beta(1-\varepsilon c)\eta}{\mu} & 0 \\ 0 & -\lambda & 0 & 0 \\ 0 & 0 & -\lambda & 0 \\ 0 & 0 & 0 & -\lambda \end{pmatrix} = 0 \quad (28)$$

$$R_C = \frac{\beta(1-\varepsilon c)\{\mu K_2 + \tau d\mu + \tau\eta K_2(1-d)\}}{\mu K_1 K_2} \quad (29)$$

Hence the basic reproduction number of our model is given by (29) which is the average number of secondary infections caused by a single infectious individual during his/her entire infectious life time.

Solution of the Model using Homotopy Perturbation Method (HPM)

$$S(t) = S_0 + \{\Lambda - K(I_{1_0} + I_{2_0} + \eta I_{3_0} - \mu)a_0\}t + \begin{Bmatrix} K(\{K(I_{1_0} + I_{2_0} + \eta I_{3_0})S_0 - K_1 I_{1_0}\}S_0 + \{\tau d I_{1_0} - K_2 I_{2_0}\}S_0 \\ +\eta\{\tau(1-d)I_{1_0} - \mu I_{3_0}\}S_0 + (\eta I_{3_0} + I_{1_0} + I_{2_0} - \mu) \\ \{\Lambda - K(I_{1_0} + I_{2_0} + \eta I_{3_0} - \mu)S_0\} \end{Bmatrix}\frac{t^2}{2} \quad (30)$$

$$I_1(t) = I_{1_0} + \{K(I_{1_0} + I_{2_0} + \eta I_{3_0})S_0 - K_1 I_{1_0}\}t + \begin{Bmatrix} (\eta e_0 + b_0 + c_0)\{\Lambda - K(b_0 + c_0 + \eta e_0 - \mu)a_0\} \\ +K(\eta e_0 + b_0 + c_0)a_0 + (\tau d b_0 - K_2 c_0) + \\ (\tau(1-d)b_0 - \mu e_0) - K_1(K(\eta e_0 + b_0 + c_0)a_0 - K_1 b_0) \end{Bmatrix}\frac{t^2}{2} \quad (31)$$

$$I_2(t) = I_{2_0} + \{\tau d I_{1_0} - K_2 I_{2_0}\}t + \left\{\tau d\{K(I_{1_0} + I_{2_0} + \eta I_{3_0})S_0 - K_1 I_{1_0}\} - K_2(\tau d I_{1_0} - K_2 I_{2_0})\right\}\frac{t^2}{2} + \ldots \quad (32)$$

$$I_3(t) = I_{3_0} + \{\tau(1-d)I_{1_0} - \mu I_{3_0}\}t + \left\{\tau(1-d)\{K(I_{1_0} + I_{2_0} + \eta I_{3_0})S_0 - K_1 I_{1_0}\} - \mu\{\tau(1-d)I_{1_0} - \mu I_{3_0}\}\right\}\frac{t^2}{2} \quad (33)$$

$$A(t) = A_0 + \{\sigma_1 I_{1_0} + \sigma_2 I_{2_0} - K_3 A_0\}t + \begin{Bmatrix}\sigma_2\{\tau d I_{1_0} - K_2 I_{2_0}\} + \sigma_1\{K(I_{1_0} + I_{2_0} + \eta I_{3_0})S_0 - K_1 I_{1_0}\} \\ -K_3\{\sigma_1 b_0 + \sigma_2 c_0 - K_3 f_0\}\end{Bmatrix}\frac{t^2}{2} \quad (34)$$

Results and Discussion

In this section, we presented some numerical simulation to monitor the dynamics of the full model (2) – (6) in order to have pictoral demonstration of the model dynamics using MAPLE 18 software.

Table 1: Baseline values for variables of the HIV/AIDS in Nigeria

S/No	variables	Values	References
1	N	90,062,386	Aaron 2021
2	S	88,452,386	Calculated
3	I_1	800,000	ASSUMED
4	I_2	20,424	ASSUMED
5	I_3	160,000	ASSUMED
6	A	629,576	ASSUMED

Baseline Values for the Parameters used in the Model

This data is estimated based on HIV/AIDS epidemiology and published data. Based on research carried out by (Abdulrahman *et al.* 2013), they reported that there is a 20% chance of effective sexual contact rate per year for sexually active individuals. This shows that $\beta = 0.2$. And due to reduced sexual transmission rate of I_3, it is assumed that $\eta = 0.9$ so that $\eta\beta = 0.18$. Furthermore, the efficacy of condom usage is reported as 0.8 (Abdulrahman *et al.* 2013). The HIV/AIDS-induced death (δ) is estimated to be 0.014 and according to the UNICEF (2020) natural mortality rate (μ) in Nigeria is 0.018. The recruitment rate is estimated as the product of the natural mortality and the total population size as $\Lambda = \mu \times N$ that is, ($\Lambda = 0.018 \times 90062386 = 162123$). The progression rate of untreated HIV infected individuals was estimated based on data gotten from (Abdulrahman, 2013) as $\sigma_1 = 0.067$ and HART resistant individuals is assumed to be $\sigma_2 = 0.05$ And lastly, the control parameters τ and d ranges between 0 and 1.

Table 2: Baseline Values for Parameters of the HIV/AIDS.

S/N	Parameters	Values	References
1	Λ	162,123	Calculated
2	β	0.2	Abdulrahman *et al.* (2013)
3	δ	0.014	Abdulrahman *et al.* (2013)
4	η	0.9	Abdulrahman *et al.* (2013)
5	ε	0.8	Abdulrahman *et al.* (2013)
6	σ_1	0.067	Abdulrahman *et al.* (2013)
7	σ_2	0.05	Assumed
8	μ	0.018	UNICEF (2020)
9	d	n(0-1)	Varies
10	τ	(0-1)	Varies
11	c	(0-1)	Varies

Simulations

In this section some numerical simulations associated with different values of the effective reproduction number of the model were presented to further justify the analytical results.

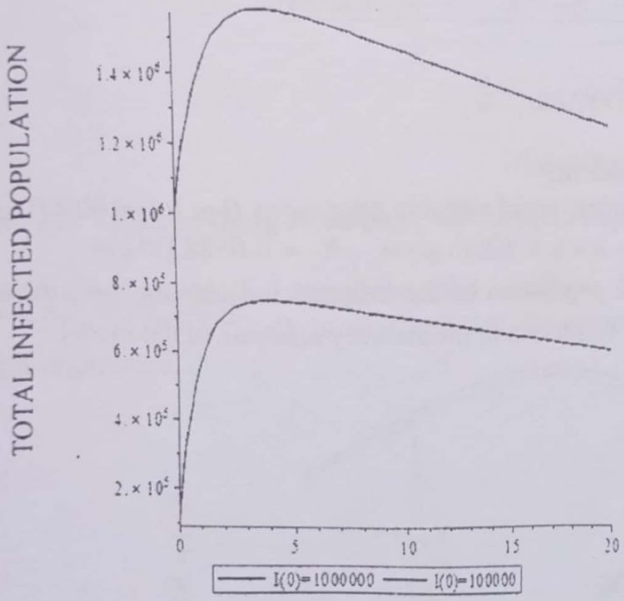

Figure 2: Validation of Analytical result on Stability

Total Number of Infected Individuals with different initial variable conditions (i.e, I(0)=1000000 and I(0)=100000. (Control parameters $\tau=0.2, d=0.25, c=0.8$ which gives ($R_c = 2.927554180$). It could be noted that irrespective of the initial population of the infected individuals, the infected population grows when $R_c > 1$.

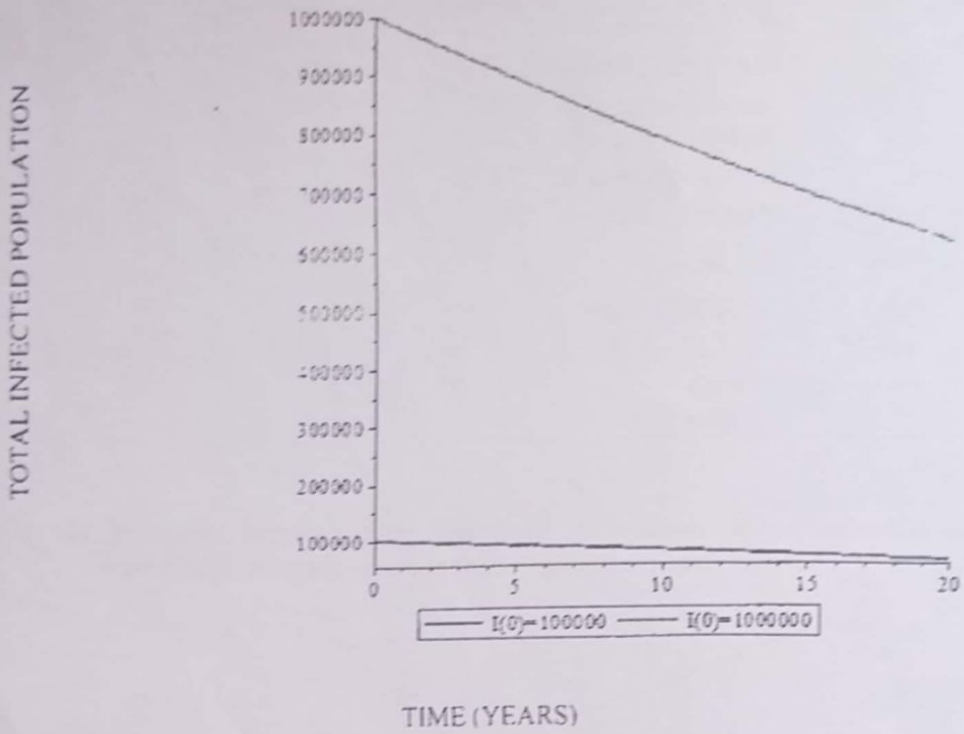

Figure 3: Validation of Analytical result on Stability

Total Number of Infected Individuals with different initial variable conditions (i.e. I(0)=100000 and I(0)=1000000). (Control parameters $r = 0, d = 0, c = 0.9$ which gives $(R_C = 0.6588235294)$.

It could be noted that irrespective of the initial population of the infected individuals, the infected population declines when $R_C < 1$. Hence it is a validation of the stability analysis of the model.

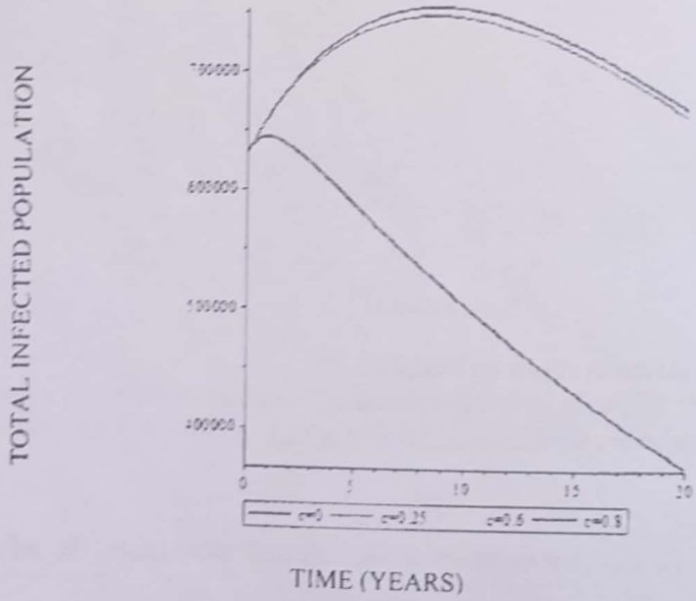

Figure 4: Effect of Condom Usage on Infected Population

Total Number of Infected Individuals with different level of compliance to condom usage (i.e, $c = 0, c = 0.25, c = 0.6, c = 0.8$) The result shows that for different levels of compliance to condom usage, there is a decline in the infected population and the higher the level of condom usage the faster the decline in the infected population.

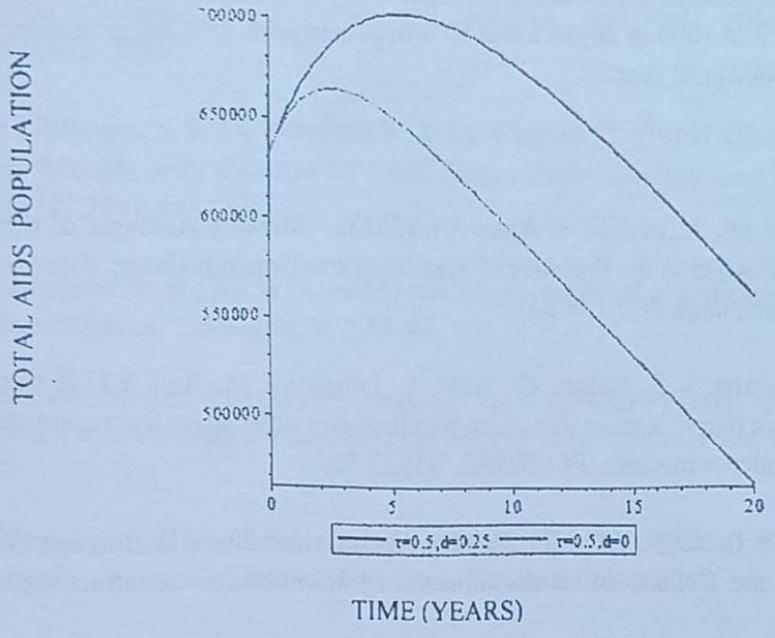

Figure 5: Effect of Drug Resistance on theAIDS Population

Effect of low drug resistance and medium treatment on the AIDS population (i.e. $\tau = 0.5, d=0.25, d=0.0$). It is observed that the lower drug resistance, the faster the decline in the AIDS population.

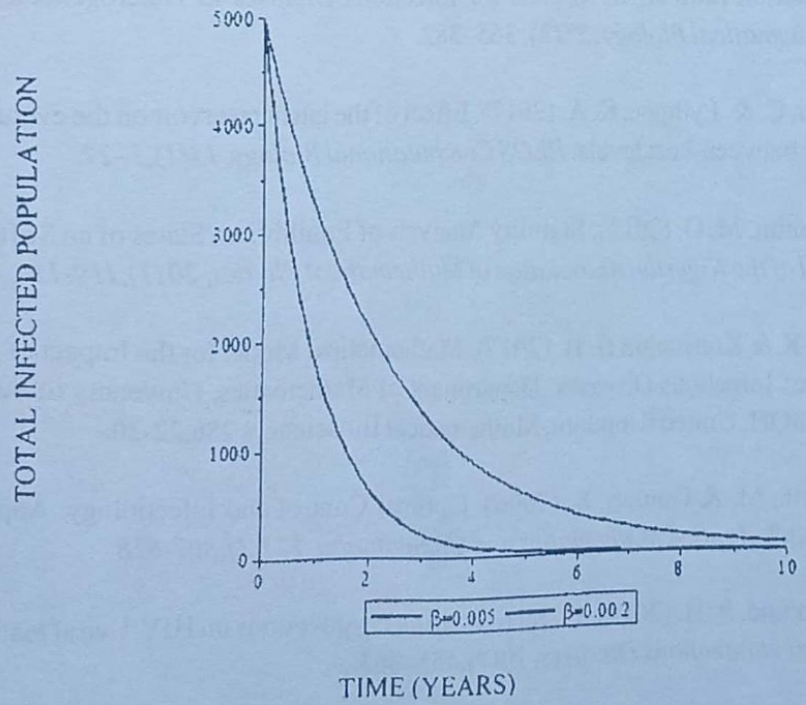

Figure 6: Validation of Analytical Result on Stability

The figure shows the effect of very low contact rate on a small infected population (i.e. $\beta_1 = 0.04, \beta_2 = 0.02$, $I(0) = 100{,}000$). It is observed that the effective contact rate has significant impact on the infected population, the lower the contact rate, the faster the decline in the infected population.

Conclusion

This research work has revealed that the best strategy in controlling HIV/AIDS is abstinence as 0.2% effective sexual contact reduces the infected population to 500 in 5years, while 80% compliance to condom usage reduces it to 1000 in 20years and 50% treatment with 25% drugs resistance reduces the infected population to 5000 in 20 years.

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