

Mathematical analysis of drug resistance in vertical transmission of HIV/AIDS

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ABSTRACT

A nonlinear mathematical model of vertical transmission of HIV/AIDS is proposed to study the effects of drug resistance in the spread of the disease. The study assumes that treatment leads to the evolution of drug resistance in some pockets of the population. We use traditional methods to determine conditions for existence and stability of disease-free and endemic equilibrium points of the model. The study showed that the burden of the disease may be reduced if the reproduction number is reduced below unity and may persist if the reproduction number is raised above unity. Furthermore, evolution of drug resistance due to treatment may change the cause of the epidemic.

Keywords: Dynamics of HIV/AIDS; Vertical Transmission; Drug Resistance

1. INTRODUCTION

Diseases can be transmitted in various ways, some of which can be classified as horizontal or vertical. In the case of HIV/AIDS, horizontal transmission can result from direct physical contact between an infected individual and a susceptible individual. In this case, HIV infection is from the infected blood, semen and vaginal fluids to the exposure individuals. This often occurs when having unprotected sex with a person who has HIV. The other risks of HIV infection comprise of sharing needles, syringes or other equipment, illicit drugs for injection or during injection drug use (when needles are shared) with an infected HIV person. Any HIV infected individual can transmit the disease irrespective of the stage or treatment status. However, high risks of infections are in the early stages of infection and during full

blown AIDS stages. These stages are associated with high viral loads.

Vertical transmission, on the other hand, results from direct transfer of a disease from an infected mother to an unborn or newly born offspring. Some of the diseases that can be transmitted vertically include chagas, dengue fever and hepatitis B. Vertical transmission of HIV/AIDS generally occurs during pregnancy, delivery or breastfeeding and may be influenced by many factors such as maternal viral load and the type of delivery [1,2]. This type of transmission is sometimes called mother-to-child transmission or ethically parent-to-child transmission. Research has shown that, not all pregnancies in HIV-infected women result in vertical transmission.

Pediatric HIV is a major contributor to high mortality rates among infants and children in sub-Saharan Africa and it remains a leading cause of deaths in children under the age of 5 years. It is estimated that one third of HIV positive infants die before their first birthday, while 50% die by their second birthday. Consequences of vertical transmission include reduction of life expectancy of HIV positive individuals [3]. Worldwide, one percent of pregnant women are HIV-positive and 95% of these HIV positive women live in sub-Saharan Africa. In the absence of treatment, approximately 25% - 50% of HIV-positive mothers will transmit the virus to their newborns during pregnancy, childbirth, or breastfeeding [4]. In sub-Saharan Africa, over 1000 newborns are infected with HIV every day, despite available medical interventions. The high rates of vertical transmission in Africa are attributed to low rates accessibility of intervention programmes and lack of adherence to the necessary medications to prevent mother-to-child transmission.

Prevention of mother-to-child transmission of HIV (PMTCT) can dramatically reduce the risk of vertical transmission. Success stories have been reported in the United States and Europe and it remains a serious chal-

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lenge to Africa [3]. Prevention of mother-to-child transmission involves the use of antiretroviral therapy (ART), caesarean section [5,6] and refraining from breastfeeding. Antiretroviral drugs are administered during pregnancy, at delivery and postnatally to the child and mothers. In resource-poor countries, short course regimens based on single dose nevirapine to the mother and infant are being used [7]. In summary, the burden of vertical transmission of HIV can be reduced by enrolling parent-to-child prevention programs which involve testing the mothers and blocking of transmission through the use of antiretroviral drugs, elective caesarean section and use of replacement infant feeding [8].

Drug resistance refers to the ability of microorganisms to adapt, survive and multiply in the presence of drugs that would normally kill or weaken them. In the case of HIV, the virus adapts and multiplies in the presence of antiretroviral (ARV) drugs often making mistakes of copying its genetic blueprint RNA. Some of these mistakes, called mutations, can make HIV resistant to one or more ARV drugs. With regard to vertical transmission, we are concerned with the potential selection of drug-resistant virus following short course of ARV treatment to prevent parent-to-child transmission (PPCT). Reports show that up to 20% of women who receive a single dose of nevirapine in HIVNET regime developed resistance [9] and this leads to the development of strains of HIV resistant to multiple combinations of ARVs.

This study therefore extends mathematical models of vertical transmission with treatment by incorporating the effects of drug resistance. The main objective of the study is to investigate the effects of vertical transmission and evolution of drug resistance in the HIV disease dynamics. The paper is arranged as follows: Section 1 introduces the study, model formulation is presented in Section 2, Section 3 presents model analysis, Section 4 presents numerical simulations while Section 5 discusses the results and presents the conclusions of the study.

2. MODEL FORMULATION

A mathematical model of a disease transmitted both horizontally and vertically in which the treatment programme results in the evolution of drug resistance is proposed and analysed. The proposed model sub-divides the population of interest into seven compartments, depending on their disease status and type of pathogen (*i.e.* resistant or wild strain). The sub-populations are the Susceptibles $S(t)$, drug resistant infectives I_R , drug sensitive infectives I_w , treated drug sensitive infective T_w , treated drug resistant infective T_R , AIDS drug sensitive A_w and AIDS drug resistant class A_R . The total population at time t is given by

$$N(t) = S(t) + I_w(t) + I_R(t) + T_w(t) + T_R(t) + A_w(t) + A_R(t) \tag{1}$$

To reduce the size of the model we relaxed the distinction between the asymptomatic (no clinical signs) and symptomatic (clinical signs) stages of HIV (WHO staging of HIV). We assumed mass action type of force of infection as opposed to standard incidence to allow for mathematical tractability of the model. This assumption is an over simplification of reality particularly highly infectious diseases like HIV. We further assume that treatment only reduces the level of infectiousness. **Table 1** below presents the definitions and descriptions of the parameters and state variables used in the model. It is worth stating that all model parameters non-negative and all have values in the open set $(0, \infty)$ except ρ which picks values in the set $[1, \infty)$.

The problem described above can be represented schematically by the flow diagram below (**Figure 1**):

The model description above leads to a system of nonlinear ordinary differential equations:

$$\begin{aligned} \frac{dS}{dt} &= \pi_s + b\varepsilon_w I_{wf} + b\varepsilon_R I_{Rf} - \lambda_w S - \lambda_R S - \mu S, \\ \frac{dI_w}{dt} &= \lambda_w S + b\tau_w \varepsilon'_w I_{wf} - (\mu + \delta_{1w} + \alpha_w) I_w, \\ \frac{dT_w}{dt} &= b\varepsilon'_w \tau'_w I_{wf} + \alpha_w I_w - (v_w + \mu + \delta_{2w} + \gamma_R + \rho\gamma_R) T_w, \\ \frac{dA_w}{dt} &= v_w T_w - (\mu + \delta_{3w} + \gamma_R) A_w, \\ \frac{dI_R}{dt} &= \lambda_R S + \gamma_R T_w + b\varepsilon'_R \tau'_R I_{Rf} - (\mu + \delta_{1R} + \alpha_R) I_R, \\ \frac{dT_R}{dt} &= \alpha_R I_R + \rho\gamma_R T_w + b\varepsilon'_R \tau'_R I_{Rf} - (v_R + \mu + \delta_{2R}) T_R, \\ \frac{dA_R}{dt} &= v_R T_R + v_R A_w - (\mu + \delta_{3R}) A_R, \end{aligned} \tag{2}$$

where

$$\begin{aligned} \lambda_w &= \beta_{1w} I_w + \beta_{2w} T_w + \beta_{3w} A_w, \\ I_{Rf} &= I_R + T_R + A_R, \\ \lambda_R &= \beta_{1R} I_R + \beta_{2R} T_R + \beta_{3R} A_R, \\ \varepsilon'_R &= 1 - \varepsilon_R, \\ I_{wf} &= I_w + T_w + A_w, \\ \text{and } \varepsilon'_w &= 1 - \varepsilon_w. \end{aligned}$$

3. MODEL ANALYSIS

System (2) is analysed to find conditions for existence

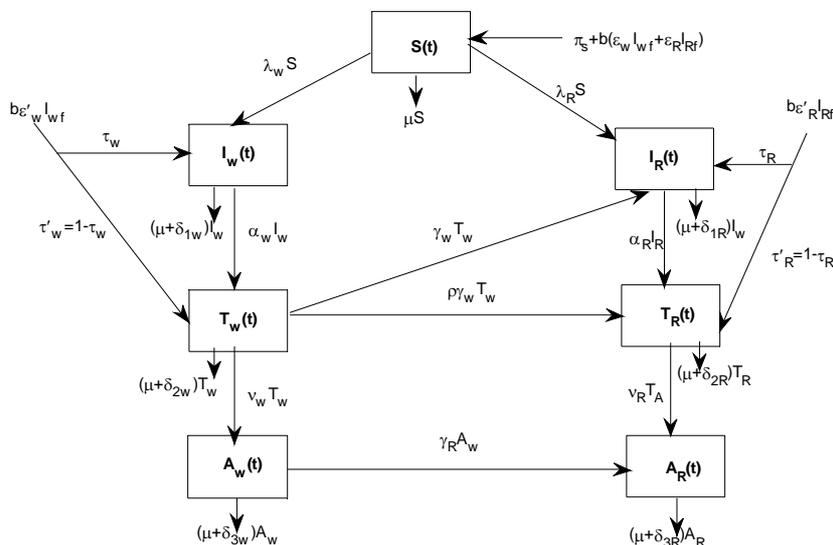


Figure 1. Vertical transmission model of HIV with drug resistance.

Table 1. Parameters and their descriptions.

Parameter	Description
ϵ_w	Proportion of offspring who are drug sensitive
ϵ_R	Proportion of offspring with drug resistance
λ_w	Force of infection of drug sensitive individuals
λ_R	Force of infection of drug resistant individuals
$\delta_{iws}, i = 1, 2, 3$	AIDS related death of infected drug sensitive, treated drug sensitive and AIDS drug sensitive respectively
$\delta_{iRs}, i = 1, 2, 3$	AIDS related death of infected drug resistant, treated drug resistant and AIDS drug resistant respectively
v_w	Progression rate from infected drug sensitive to AIDS drug sensitive
v_R	Progression rate from infected drug resistant to AIDS drug resistant
α_w	Progression rate of infected drug sensitive to treated drug sensitive
α_R	Progression rate of infected drug resistant to treated drug resistant
γ_w	Evolution rate of drug resistant virus
ρ	Modification parameter

and stability of disease free and endemic equilibrium points. This analysis of the model allows us to determine the impact of drug resistant virus in the treatment and vertical transmission on the transmission of HIV/AIDS infection in a population characterized in terms of the reproductive number R_0 .

3.1. Positivity of Solutions

Adding equations of system (2) we obtain an equation governing changes in the total population

$$\dot{N} = \pi_s - \mu N - b(I_{wf} + I_{Rf}) - \alpha_w I_w - \alpha_R I_R - \delta_{2w} T_w - \delta_{2R} T_R - \delta_{3w} A_w - \delta_{3R} A_R$$

In the absence of HIV infection the total population converges to π_s / μ . It follows that the $\limsup_i N(t) \leq \pi_s / \mu$ and it suffices to study system (2) in an invariant set

$$\Omega = \{(S, I_w, I_R, T_w, T_R, A_w, A_R) \in \mathbb{R}_+^7 \mid \pi_s / \mu\}$$

We now show that the initial data of $(S, I_w, I_R, T_w, T_R, A_w, A_R)$ which are non-negative lead to solutions that remain non-negative for all $t \geq 0$.

Theorem 3.5

Let

$$\{S(0) > 0, I_w(0) \geq 0, T_w(0) \geq 0, A_w(0) \geq 0, I_R(0) \geq 0, T_R(0) \geq 0, A_R(0) \geq 0\} \in F$$

where $F \subseteq \Omega$. Then the solutions $\{S(t), I_w(t), T_w(t), A_w(t), I_R(t), T_R(t), A_R(t)\}$ of the model system of Equation (2) are positive $\forall t \geq 0$.

Proof

From the first equation of (2), we have

$$\frac{dS}{dt} \geq -(\lambda_w + \lambda_R + \mu)S, \int_0^t \frac{1}{S} dS \geq -\int_0^t (\lambda_w + \lambda_R + \mu) ds,$$

which gives

$$S(t) \geq S(0) e^{-\int_0^t (\lambda_w + \lambda_R + \mu) ds} = S(0) e^{-(\lambda_w + \lambda_R + \mu)t} \geq 0.$$

As $t \rightarrow \infty$ we obtain $S(t) \geq 0$. Hence all feasible

solution of system (2) enter the region $\{S(t), I_w(t), T_w(t), A_w(t), I_R(t), T_R(t), A_R(t)\} \in F$. Similar proofs can be established for the positivity of $I_w, T_w, A_w, I_R, T_R, A_R$.

Thus, the equations of system (2) are well posed.

3.2. Steady State Solutions

The equilibrium solutions of the model (2) are obtained by setting the right hand side of system (2) to zero, to solve the following system of non-linear equations:

$$\begin{aligned} \pi_s + b\varepsilon_w I_{wf}^* + b\varepsilon_R I_{Rf}^* - \lambda_w S^* - \lambda_R S^* - \mu S^* &= 0, \\ \lambda_w S^* + b\tau_w \varepsilon'_w I_{wf}^* - (\mu + \delta_{1w} + \alpha_w) I_w^* &= 0, \\ b\varepsilon'_w \tau'_w I_{wf}^* + \alpha_w I_w^* - (\nu_w + \mu + \delta_{2w} + \gamma_R + \rho\gamma_R) T_w^* &= 0, \\ \nu_w T_w^* - (\mu + \delta_{3w} + \gamma_R) A_w^* &= 0, \\ \lambda_R S^* + \gamma_R T_w^* + b\varepsilon'_R \tau'_R I_{Rf}^* - (\mu + \delta_{1R} + \alpha_R) I_R^* &= 0, \\ \alpha_R I_R^* + \rho\gamma_R T_w^* + b\varepsilon'_R \tau'_R I_{Rf}^* - (\nu_R + \mu + \delta_{2R}) T_R^* &= 0, \\ \nu_R T_R^* + \nu_R A_w^* - (\mu + \delta_{3R}) A_R^* &= 0. \end{aligned} \tag{3}$$

From the equation of A_w^* we have $A_w^* = P_0 T_w^*$ where

$$P_0 = \frac{\nu_w}{\mu + \gamma_R + \delta_{3w}}$$

Substituting A_w^* in the expressions for I_{wf}^* and λ_{wf}^* yields

$$I_{wf}^* = I_w^* + (1 + P_0) T_w^*$$

and

$$\lambda_{wf}^* = \beta_{1w} I_w^* + (\beta_{2w} + P_0 \beta_{3w}) T_w^*$$

which upon substitution in the equations for I_w^* and T_w^* gives $T_w^* = P_1 I_w^*$ with $I_{wf}^* = P_2 I_w^*$ and $\lambda_{wf}^* = P_3 I_w^*$ where

$$P_2 = 1 + (1 + P_0) P_1$$

and

$$P_1 = \frac{(b\varepsilon'_w \tau'_w + \alpha_w)}{\nu_w + \mu + \delta_{2w} + \nu_R + \gamma_R + \rho\gamma_R - b\varepsilon'_w \tau'_w (1 + P_0)}$$

Defining

$$\mathfrak{R}_{0w} = \frac{\beta_{1w} + (\beta_{2w} + P_0 \beta_{3w}) P_1}{\mu + \alpha_w + \delta_{1w} - b\tau_w \varepsilon'_w P_2}$$

to be threshold parameter due to the wild strain, and then substituting for I_{wf}^* and λ_{wf}^* in the equation for S^* we obtain $I_w^* = 0$ or

$$S^* = \frac{1}{\mathfrak{R}_{0w}}$$

The solution $I_w^* = 0$ yields $A_R^* = Q_0 T_R^*$, where

$$Q_0 = \frac{\nu_R}{\mu + \delta_{3R}}$$

Substituting A_R^* in the expressions for I_{Rf}^* and λ_R we get

$$\lambda_R = \beta_{1R} I_R^* + (\beta_{2R} + Q_0 \beta_{3R}) T_R^*$$

and

$$I_{Rf}^* = I_R^* + (1 + Q_0) T_R^*$$

The expression for I_{wf}^* together with an equation for I_R^* give $T_R^* = Q_1 I_R^*$ where

$$Q_1 = \frac{\alpha_R + b\varepsilon'_R \tau'_R}{\mu + \delta_{2R} + \nu_R - b\varepsilon'_R \tau'_R (1 + Q_0)}$$

provided that

$$\mu + \delta_{2R} + \nu_R > b\varepsilon'_R \tau'_R (1 + Q_0)$$

With this expression for T_R^* the expressions for I_{Rf}^* and λ_R reduce to $\lambda_R = \eta_R I_R^*$ and $I_{Rf}^* = Q_2 I_R^*$ where

$$\eta_R = \beta_{1R} + (\beta_{2R} + Q_0 \beta_{3R}) Q_1$$

and

$$Q_2 = 1 + (1 + Q_0) Q_1$$

Substituting for I_{Rf}^* and λ_R in the equation for I_R^* we obtaining $I_R^* = 0$

or

$$S^* = \frac{1}{\mathfrak{R}_{0R}}$$

3.2.1. Disease-Free Equilibrium

The solution $I_w^* = 0$ and $I_R^* = 0$ lead to the disease-free equilibrium point

$$E_0 = \left(\frac{\pi_s}{\mu}, 0, 0, 0, 0, 0 \right)$$

3.2.2. Wild Strain-Free Equilibrium

The solutions $I_w^* = 0$

and

$$S^* = \frac{1}{\mathfrak{R}_{0R}}$$

lead to a drug resistant strain endemic equilibrium given by $E_R = (S^*, 0, 0, 0, I_R^*, T_R^*, A_R^*)$ with coordinates

$$S^* = \frac{1}{\mathfrak{R}_{0R}}, T_R^* = Q_1 I_R^*, A_R^* = Q_0 Q_1 I_R^*$$

and

$$I_R^* = \left(\frac{\mu}{\mu + \alpha_R + \delta_{1R} - b(\tau_R + \tau'_R \varepsilon_R) Q_2} \right) \left(\frac{1}{\mathfrak{R}_{0R}} \right) (\mathfrak{R}_0^R - 1);$$

$$\mathfrak{R}_0^R = \frac{\pi_s}{\mu} \mathfrak{R}_{0R}$$

3.2.3. Drug Resistant Strain-Free Equilibrium

The solutions $I_w^* \neq 0$ and

$$S^* = \frac{1}{\mathfrak{R}_{0R}}$$

lead to an drug resistant strain endemic equilibrium given by

$$E_w = (S^*, I_w^*, T_w^*, A_w^*, 0, 0, 0)$$

with coordinates

$$S^* = \frac{1}{\mathfrak{R}_{0w}}, T_w^* = P_1 I_w^*, A_w^* = P_0 P_1 I_w^*,$$

and

$$I_w^* = \left(\frac{\mu}{\mu + \alpha_w + \delta_{1w} - b(\tau_w + \tau'_w \epsilon'_w) P_2} \right) \left(\frac{1}{\mathfrak{R}_{0w}} \right) (\mathfrak{R}_0^w - 1);$$

$$\mathfrak{R}_0^w = \frac{\pi_s}{\mu} \mathfrak{R}_{0w}$$

3.2.4. Coexistence of Wild and Resistant Strains

In this case, we consider $I_w^* \neq 0$ and

$$S^* = \frac{1}{\mathfrak{R}_{0w}}$$

The equation for A_R^* leads to

$$A_R^* = Q_0 T_R^* + Q_0 P_0 P_1 I_w^*,$$

where Q_0 , P_0 and P_1 are as defined above. Substituting A_R^* in the expressions for I_{Rf}^* and λ_w^* yields

$$\lambda_R = \beta_{1R} I_R^* + (\beta_{2R} + Q_0 \beta_{3R}) T_R^* + Q_0 P_0 P_1 \beta_{3R} I_R^*$$

and

$$I_{Rf}^* = I_R^* + (1 + Q_0) T_R^* + Q_0 P_0 P_1 I_w^*$$

Substitution of I_{Rf}^* and λ_R^* in the equation for I_R^* results in

$$T_R^* = Q_1 I_R^* + Q_3 I_w^*,$$

where

$$Q_1 = \frac{\alpha_R + b\tau'_R \epsilon'_R}{\mu + \alpha_R + \delta_{2R} - b\tau'_R \epsilon'_R (1 + Q_0)}$$

and

$$Q_3 = \frac{(\rho\gamma_R + Q_0 P_0 b\tau'_R \epsilon'_R) P_1}{\mu + \alpha_R + \delta_{2R} - b\tau'_R \epsilon'_R (1 + Q_0)}$$

The expression for T_R^* gives to $\lambda_R = \eta_R I_R^* + \eta_{wR} I_w^*$ and

$$I_{Rf}^* = Q_2 I_R^* + Q_4 I_w^*$$

where

$$\eta_{wR} = Q_3 \beta_{2R} + Q_0 (P_0 P_1 + Q_3) \beta_{3R}$$

and

$$Q_4 = Q_0 P_0 P_1 + Q_3 (1 + Q_0)$$

Let

$$\mathfrak{R}_{0R} = \frac{\beta_{1R} + (\beta_{2R} + (1 + Q_0) \beta_{3R})}{\mu + \alpha_R + \delta_{1R} - b\tau'_R \epsilon'_R Q_2}$$

be the threshold parameter due to drug resistance and

$$Q_5 = \frac{\mu + \alpha_R + \delta_{1R} - b\tau'_R \epsilon'_R Q_2}{\eta_{wR} + (\gamma_R P_1 + b\tau'_R \epsilon'_R Q_2) \mathfrak{R}_{0w}}$$

Then we establish a relationship between I_w^* and I_R^* as

$$I_w^* = Q_5 (\mathfrak{R}_{0w} - \mathfrak{R}_{0R}) I_R^*$$

Clearly, $\mathfrak{R}_{0w} > \mathfrak{R}_{0R}$ and result confirms the findings in literature which claims that the virulence of resistant strain is weak than the wild strain. The results above and the equation for S^* yield

$$I_R^* = \frac{\mu (\mathfrak{R}_0^R - 1)}{Q_6 (\mathfrak{R}_{0w} - \mathfrak{R}_{0R}) + Q_7},$$

where

$$Q_6 = Q_5 (\eta_w - b\epsilon_R P_2 \mathfrak{R}_{0w} + \eta_{wR} - b\epsilon_R Q_2 \mathfrak{R}_{0w})$$

and

$$Q_7 = \eta_R - b\epsilon_R Q_2 \mathfrak{R}_{0w}$$

satisfying the conditions

$$\eta_w > b\epsilon_R P_2 \mathfrak{R}_{0w}, \eta_{wR} > b\epsilon_R Q_2 \mathfrak{R}_{0w} \text{ and } \eta_R > b\epsilon_R Q_2 \mathfrak{R}_{0w}$$

3.2.5. The Model Reproduction Numbers (Thresholds)

Suppose

$$\mu_2 = \frac{\alpha_w}{\mu + \alpha_w + \delta_{2w}}, \mu_3 = \frac{\nu_w}{\mu + \gamma_w + \rho\gamma_w + \nu_w + \delta_{2w}} \mu_2,$$

$$\mathfrak{R}_{1h}^w = \frac{K\beta_{1w}}{\mu + \alpha_w + \delta_{1w}}, \mathfrak{R}_{1v}^w = \frac{b\tau'_R \epsilon'_R}{\mu + \alpha_w + \delta_{1w}},$$

$$\mathfrak{R}_{2h}^w = \frac{K\beta_{2w}}{\mu + \gamma_w + \rho\gamma_w + \nu_w + \delta_{2w}},$$

$$\mathfrak{R}_{2v}^w = \frac{b\tau'_R \epsilon'_R}{\mu + \gamma_w + \rho\gamma_w + \nu_w + \delta_{2w}},$$

$$\mathfrak{R}_{3h}^w = \frac{K\beta_{3w}}{\mu + \delta_{3w}}, \mathfrak{R}_{3v}^w = \frac{b\tau'_R \epsilon'_R}{\mu + \delta_{3w}},$$

$$\mathfrak{R}_{1vT}^w = \frac{b\tau'_R \epsilon'_R}{\mu + \alpha_w + \delta_{2w}},$$

$$\mathfrak{R}_{2vT}^w = \frac{b\tau'_R \epsilon'_R}{\mu + \gamma_w + \rho\gamma_w + \nu_w + \delta_{2w}}, \text{ and } \mathfrak{R}_{3vT}^w = \frac{b\tau'_R \epsilon'_R}{\mu + \delta_{3w}}.$$

Then we can express the generation of secondary infections due to horizontal transmission as

$$\mathfrak{R}_{0h}^w = \mathfrak{R}_{1h}^w + \mu_2 \mathfrak{R}_{2h}^w + \mu_3 \mathfrak{R}_{0h}^w$$

and vertical transmission as

$$\mathfrak{R}_{0v}^w = \mathfrak{R}_{1v}^w + \mu_2 \mathfrak{R}_{2v}^w + \mu_3 \mathfrak{R}_{0v}^w$$

with the net effects of the transmission due to the wild

strain given by $\mathfrak{R}_0^w = \mathfrak{R}_{0h}^w + \mathfrak{R}_{0v}^w$. The reproduction number of the model is given by

$$R_0 = \max(R_0^w, R_0^r) \text{ where } R_0^w = \frac{a_{1i} + \sqrt{a_{1i}^2 - 4a_{0i}a_{2i}}}{2a_{0i}}$$

with

$$\begin{aligned} a_{0i} &= 1, \mathfrak{R}_{jhw}^w = \sum_{j=1}^3 (\mathfrak{R}_{vh}^w + \mathfrak{R}_{jv}^w); \\ a_{1i} &= \mathfrak{R}_{1hv}^i + \mu_2 \mathfrak{R}_{2hv}^i + \mu_3 \mathfrak{R}_{3hv}^i + \mathfrak{R}_{2v}^i + \mu_2 \mathfrak{R}_{3v}^i, \\ a_{2i} &= \mathfrak{R}_{2vT}^i \mathfrak{R}_{1hv}^i - \mathfrak{R}_{1vT}^i \mathfrak{R}_{2hv}^i + \mu_3 (\mathfrak{R}_{3vT}^i \mathfrak{R}_{1hv}^i - \mathfrak{R}_{1vT}^i \mathfrak{R}_{3hv}^i) \end{aligned}$$

and $a_{1i}^2 > 4a_{0i}a_{2i}$ for $i = w, R$. The parameter R_0 is defined as the average number of secondary infections generated by introducing an infected individual (with either wild or resistant strain) in a wholly susceptible population. The threshold parameters \mathfrak{R}_{jvT}^i for $i = w, R$ and $j = 1, 2, 3$, are the demographic replacement of secondary infections due to vertical transmission by individuals identified and enrolled on antiretroviral therapy (ART) from childhood, while \mathfrak{R}_{jv}^i for $i = w, R$ and $j = 1, 2, 3$ are the demographic replacement of secondary infections due to vertical transmission by offsprings who progress from birth to adulthood without treatment.

3.3. Local Stability of Disease-Free Equilibrium Point

Evaluating at the disease-free equilibrium point

$$E_0 = \left(\frac{\pi_s}{\mu}, 0, 0, 0, 0, 0 \right),$$

the system has the Jacobian matrix J_{E_0} , given by

$$J_0 = \begin{pmatrix} A_{11} & A_{12} & A_{13} \\ \mathbf{0} & A_{22} & \mathbf{0} \\ \mathbf{0} & A_{32} & A_{33} \end{pmatrix}$$

where

$$\begin{aligned} A_{11} &= -\mu, \\ A_{12} &= b\varepsilon_w - \beta_{1w}, b\varepsilon_w - \beta_{2w}, b\varepsilon_w - \beta_{3w}, \\ A_{13} &= b\varepsilon_R - \beta_{1R}, b\varepsilon_R - \beta_{2R}, b\varepsilon_R - \beta_{3R} \\ A_{22} &= \begin{pmatrix} \beta_{1w} - M_{1w} + b\tau_w \varepsilon'_w & \beta_{2w} + b\tau_w \varepsilon'_w & \beta_{3w} + b\tau_w \varepsilon'_w \\ b\varepsilon'_w \tau'_w + \alpha_w & b\varepsilon'_w \tau'_w - M_{2w} & b\varepsilon'_w \tau'_w \\ 0 & \nu_w & -M_{3w} \end{pmatrix}, \\ A_{33} &= \begin{pmatrix} \beta_{1R} - M_{1R} + b\tau_R \varepsilon'_R & \beta_{2R} + b\tau_R \varepsilon'_R & \beta_{3R} + b\tau_R \varepsilon'_R \\ b\varepsilon'_R \tau'_R + \alpha_R & b\varepsilon'_R \tau'_R - M_{2R} & b\varepsilon'_R \tau'_R \\ 0 & \nu_R & -M_{3R} \end{pmatrix} \\ \text{and } A_{32} &= \begin{pmatrix} 0 & \gamma_w & 0 \\ 0 & \rho\gamma_w & 0 \\ 0 & 0 & \nu_R \end{pmatrix}. \end{aligned}$$

We note from matrix A_{11} that $\lambda_1 = -\mu$ and the other eigenvalues can be found from solving the charac-

teristic polynomials of the block matrices A_{22} and A_{33} . The characteristic polynomial of the block matrix A_{22} is given by,

$$\lambda^3 - p_2 \lambda^2 + p_1 \lambda + p_0 = 0,$$

where

$$\begin{aligned} p_2 &= M_{3w} - g_5 + M_{2w} - g_1 + M_{1w}, \\ p_1 &= -g_6 \nu_w - g_5 M_{3w} + M_{2w} M_{3w} - g_1 M_{3w} + M_{1w} M_{3w} \\ &\quad - g_2 g_4 + g_1 g_5 - g_5 M_{1w} - g_1 M_{2w} + M_{1w} M_{2w}, \\ p_0 &= -\nu_w g_4 g_3 + \nu_w g_6 g_1 - \nu_w g_6 M_w - g_4 g_2 M_{3w} + g_1 g_5 M_{3w} \\ &\quad - g_5 M_w M_{3w} - g_1 M_{2w} M_{3w} + M_w M_{2w} M_{3w} \end{aligned}$$

with

$$\begin{aligned} g_1 &= \beta_{1w} + b\tau_w \varepsilon'_w, g_2 = b\varepsilon'_w \tau'_w, g_3 = b\varepsilon'_w \tau'_w, \\ g_4 &= b\varepsilon'_w \tau'_w + \alpha_w, g_5 = \beta_{2w} + b\tau_w \varepsilon'_w, g_6 = \beta_{3w} + b\tau_w \varepsilon'_w. \end{aligned}$$

After some manipulations it can be shown that the expression for p_0 is written as

$$p_0 = Z_1 (1 - R_{0,C}(w)), \tag{4}$$

where

$$\begin{aligned} Z_1 &= \nu_w g_6 g_1 + g_1 g_5 M_{3w} + M_w M_{2w} M_{3w}, \\ R_{0,C}(w) &= \frac{\nu_w g_4 g_3 + \nu_w g_6 M_w + g_4 g_2 M_{3w} + g_5 M_{1w} M_{3w} + g_1 M_{2w} M_{3w}}{\nu_w g_6 g_1 + g_1 g_5 M_{3w} + M_{1w} M_{2w} M_{3w}}. \end{aligned} \tag{5}$$

The threshold $R_{0,C}(w)$ is called the basic reproduction number for wild virus type for the system (2).

The characteristic polynomial of block matrix A_{33} is given by,

$$\lambda^3 - h_2 \lambda^2 + h_1 \lambda + h_0 = 0,$$

where

$$\begin{aligned} h_0 &= -\nu_R n_4 h_3 + \nu_R n_6 n_1 - \nu_w n_6 M_{1R} - n_4 n_2 M_{3R} + n_1 n_5 M_{3R} \\ &\quad - n_5 M_R M_{3R} - n_1 M_{2R} M_{3R} + M_{1R} M_{2R} M_{3R}, \\ h_1 &= -n_6 \nu_R - n_5 M_{3R} + M_{2R} M_{3R} - n_1 M_{3R} + M_{1R} M_{3R} \\ &\quad - n_2 n_4 + n_1 n_5 - n_5 M_{1R} - n_1 M_{2R} + M_{1R} M_{2R}, \\ h_2 &= M_{3R} - g_5 + M_{2R} - g_1 + M_{1R}, \\ n_1 &= \beta_{1R} + b\tau_R \varepsilon'_R, n_2 = b\varepsilon'_R \tau'_R, n_3 = b\varepsilon'_R \tau'_R, \\ n_4 &= b\varepsilon'_R \tau'_R + \alpha_R, n_5 = \beta_{2R} + b\tau_R \varepsilon'_R, n_6 = \beta_{3R} + b\tau_R \varepsilon'_R. \end{aligned}$$

The expression for h_0 can be written as

$$h_0 = Z_2 (1 - \mathfrak{R}_{0,C}(R)), \tag{6}$$

where

$$\begin{aligned} Z_2 &= \nu_R n_6 n_1 + n_1 n_5 M_{3R} + M_{1R} M_{2R} M_{3R}, \\ \mathfrak{R}_{0,C}(R) &= \frac{\nu_R n_4 n_3 + \nu_R n_6 M_{1R} + n_4 n_2 M_{3R} + n_5 M_{1R} M_{3R} + n_1 M_{2R} M_{3R}}{\nu_R n_6 n_1 + n_1 n_5 M_{3R} + M_{1R} M_{2R} M_{3R}}. \end{aligned} \tag{7}$$

The threshold $\mathfrak{R}_{0,C}(R)$ is called the basic reproduction number for drug resistant virus type for the system (2).

From Equation (5) and (7), we now have the effective reproduction number of the model (denoted by $\mathfrak{R}_{0,C}(wR)$) given by

$$R_{0,C}(wR) = \max \{R_{0,C}(w), \mathfrak{R}_{0,C}(R)\}$$

$$M_{1w} = \mu + \delta_{3w} + \alpha_w, M_{1R} = \mu + \delta_{3R} + \alpha_R,$$

$$M_{2w} = v_w + \mu + \delta_{2w} + \gamma_R + \rho\gamma_R, M_{2R} = v_R + \mu + \delta_{2R},$$

$$M_{3w} = \mu + \delta_{3w} + v_R, M_{3R} = \mu + \delta_{3R}.$$

Theorem 1

The disease-free equilibrium point of the vertical transmission model (2) with drug resistance is locally asymptotically stable if $R_{0,C}(wR) < 1$ and unstable if $R_{0,C}(wR) > 1$.

4. NUMERICAL SIMULATIONS

In order to illustrate some of the analytical results of the study, numerous numerical simulations of the model (2) are carried out using a set of reasonable parameter values given in **Table 2** below.

Table 2. Parameter values used in numerical simulation.

Parameters	Values	Source
π_s	100,000	[10]
b	0.06	[11]
μ	0.03	[12]
ε_w and ε_R	$\varepsilon_w = 0.7$ $\varepsilon_R = 0.7$	[11] [11]
τ_w and τ_R	$\tau_w = 0.2$ $\tau_R = 0.3$	Estimated Estimated
$\delta_{iw}, i = 1, 2, 3$	$\delta_{1w} = 0.111$ $\delta_{2w} = 0.222$ $\delta_{3w} = 0.333$	Estimated Estimated [10]
$\delta_{iR}, i = 1, 2, 3$	$\delta_{1R} = 0.4$ $\delta_{2R} = 0.5$ $\delta_{3R} = 0.6$	Estimated Estimated Estimated
v_w and v_R	$v_w = 0.05$ $v_R = 0.1$	[12] [13]
α_w and α_R	$\alpha_w = 0.6$ $\alpha_R = 0.7$	[14] Estimated
γ_w	$\gamma_w = 0.08$	Estimated
ρ	$\rho = 1.2$	Estimated
β_i	$\beta_{1w} = 0.2$	[15]
	$\beta_{2w} = 0.08$	[15]
	$\beta_{3w} = 0.12$	Estimated
	$\beta_{1R} = 0.3$	Estimated
	$\beta_{2R} = 0.09$ $\beta_{3R} = 0.13$	Estimated Estimated

However these parameters may (or may not) be biologically feasible.

Figure 2 below shows the variations of the seven classes of HIV/AIDS model with drug resistance.

From **Figure 2** it can be seen is that, infective population is increasing. This leads into the decrease in susceptible class.

Figure 3 below shows the effects of rate of HIV Free children born with wild sensitive virus.

Figure 3 shows that as ε_w increases, individuals in AIDS and treated classes with drug resistant virus decrease. However, the number of susceptible individuals increases.

Figure 4 below shows the effects of Rate of HIV Free Children Born with Drug Resistant Virus.

Figure 4 shows that as the proportion of children who are drug resistant born HIV negative increases, the numbers of populations in the drug resistant class and treated drug resistant class decrease.

Figure 5 below depicts the behaviour of the AIDS population with both wild and resistant strains, and treated population with resistant strain as influence by changes in the progression rates of drug resistant individuals to AIDS.

From **Figure 5** it is seen that at high progression rates, the three classes reach their peaks much faster than at low values of progression rates, with AIDS class having the highest peak and infective population having the lowest peak.

Figure 6 shows the effects of variation of progression rates to I_R and T_R when γ_w is varied.

Figure 6 shows that increasing γ_w leads to decrease in number of individuals in the treated and infected with wild virus classes. However, individuals in I_R , T_R and A_R increase as γ_w increases.

Figure 7 below show the effects of treatment rates of

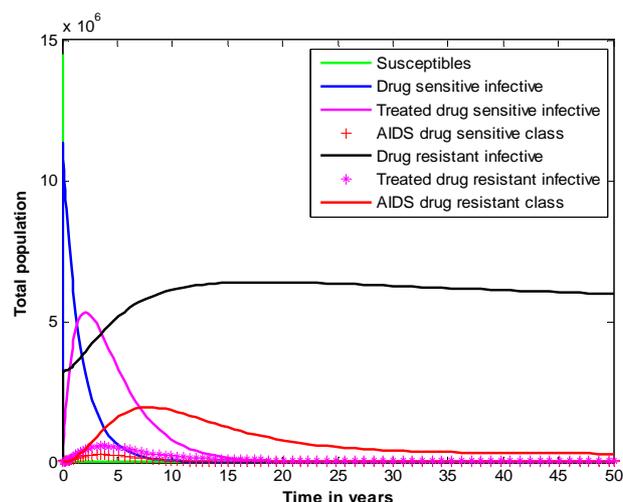


Figure 2. Illustration of the changes in seven state variables of full HIV/AIDS model with drug resistance.

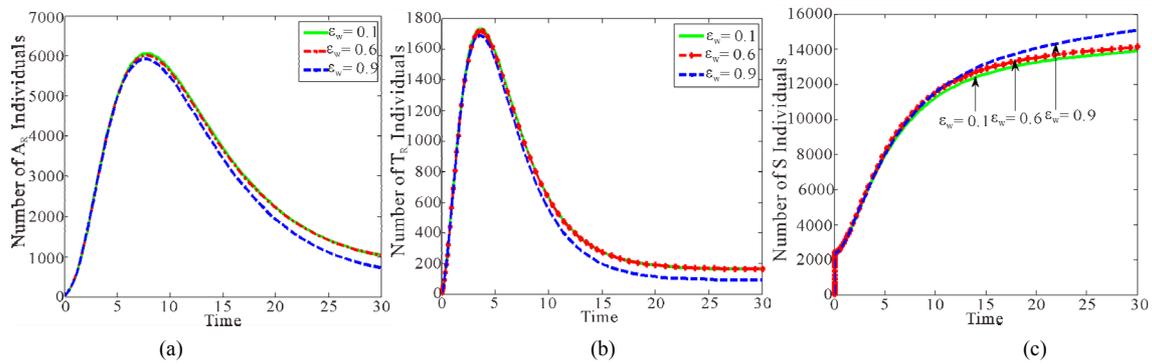


Figure 3. Effects of variation of proportion of children born with wild sensitive virus.

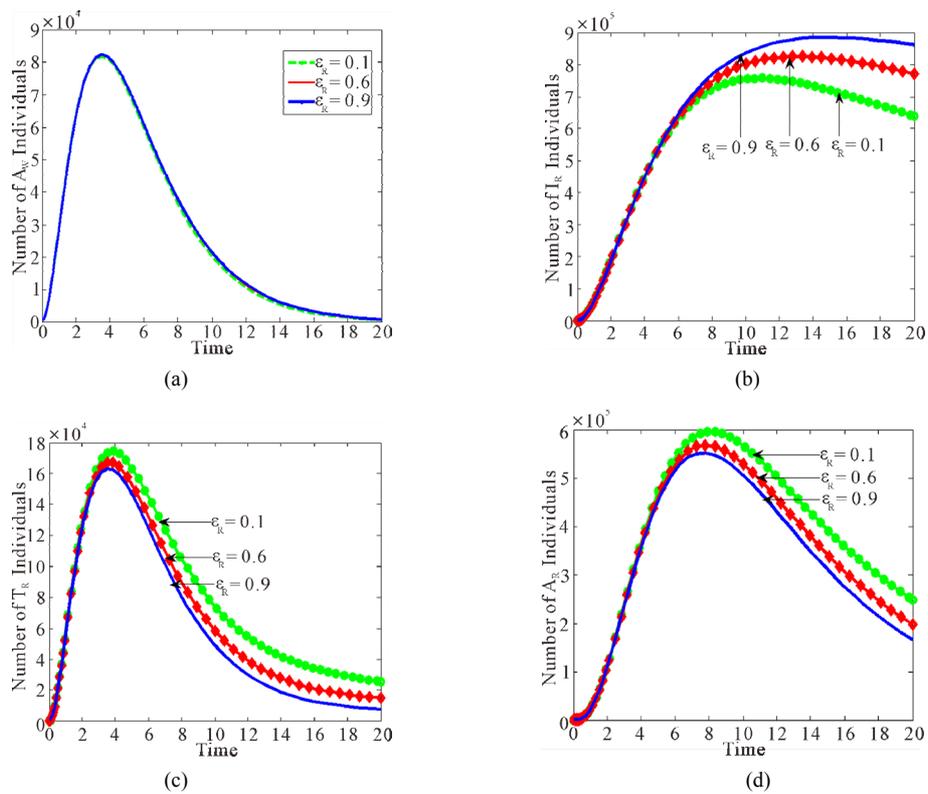


Figure 4. Dynamics of drug resistance influenced by vertical transmission with ϵ_R being varied.

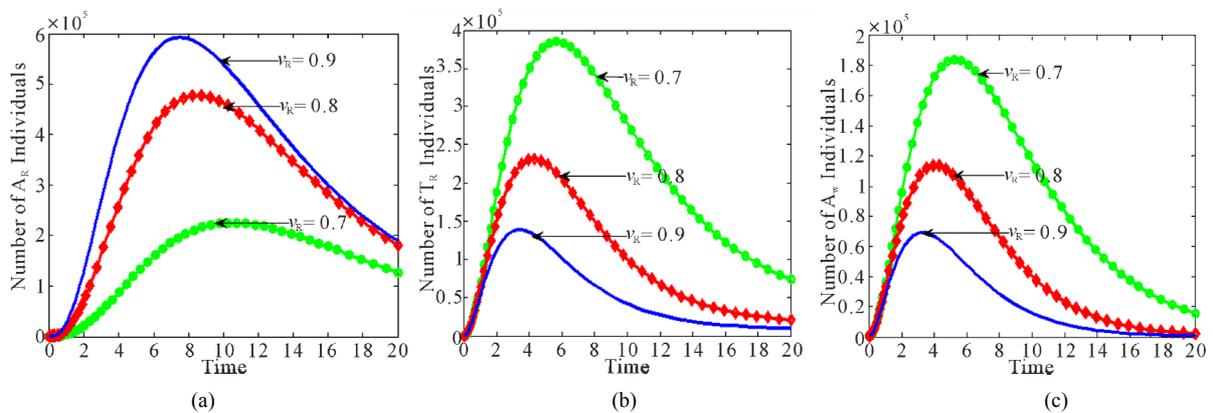


Figure 5. Effects of rate of progression to AIDS on vertical transmission.

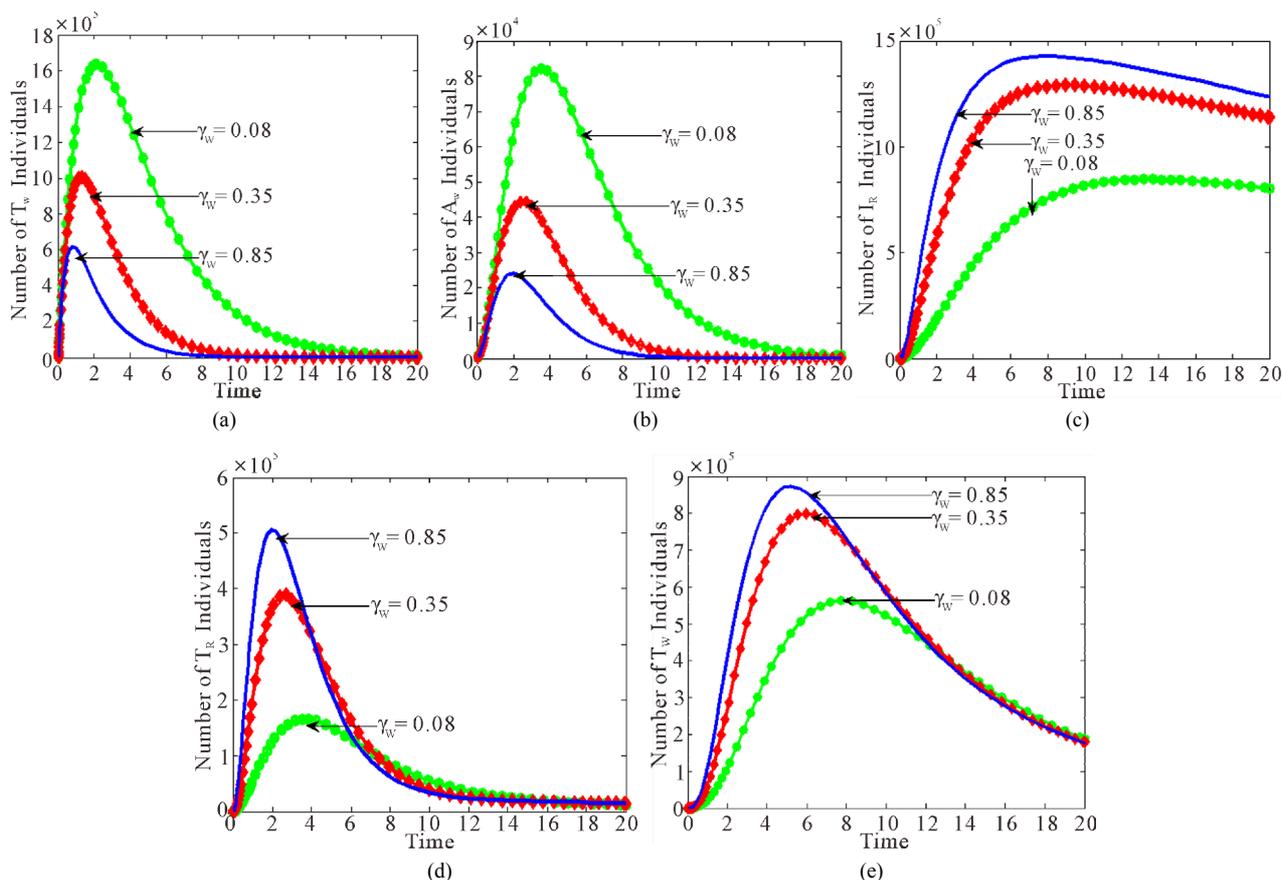


Figure 6. Effects of variation of progression rates to I_R and T_R when γ_w varied.

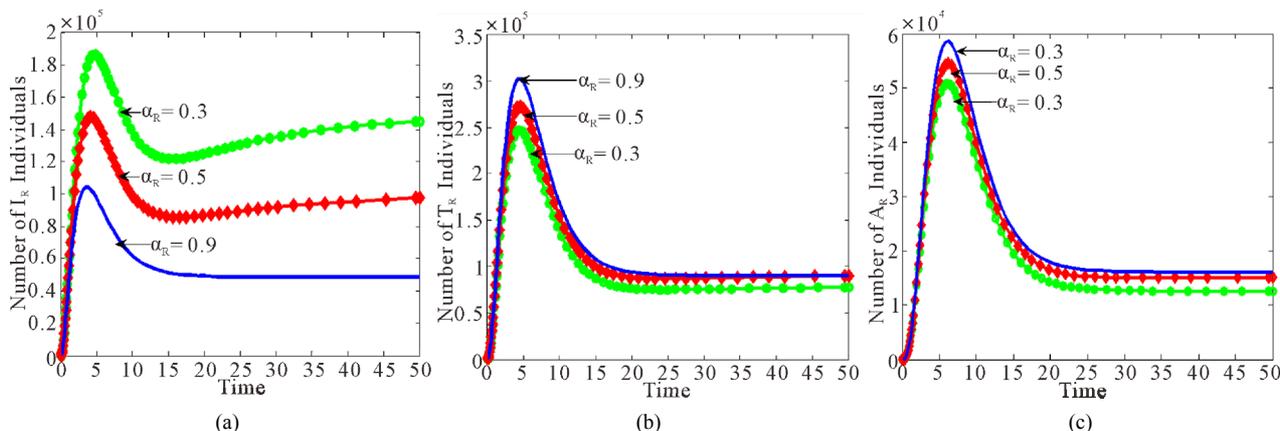


Figure 7. Effects of treatment rates of infected individuals with drug resistant virus as α_r varies.

infected individuals with drug resistant virus as α_r varies.

As the rate of treatment, α_r increases, the number of individuals infected with drug resistant virus decreases. From **Figure 7(c)**, as the rate of treatment increases, the number of AIDS patients with drug resistance increase. It is also noted that the peaks for different values of α_r occur at the same time as for I_R , T_R and A_R classes.

5. DISCUSSION AND CONCLUSIONS

In this paper, a non-linear mathematical model to study the transmission of HIV/AIDS in a population of varying size with vertical transmission and drug resistance was proposed and analysed. Both qualitative and numerical analysis of the model was done. The disease-free and endemic equilibrium points were obtained and their stabilities were investigated. A numerical study of the mo-

del has been conducted to see the effect of certain key parameters on the spread of the disease. It was established that the disease-free equilibrium is locally asymptotically stable if the basic reproduction number $R_{0,C}(wR) < 1$ and unstable if $R_{0,C}(wR) > 1$ and the infection persists in the population.

The results have shown that treatment may increase drug resistance among treated individuals. The results further showed that increase in the rate of children born with HIV with drug resistance leads to increase of the infected individuals with drug resistance and will in long run lead to increase in the AIDS population with drug resistance. It was noted that drug resistant virus is emerging in some of the individuals who are on ARV treatment. This will in the long run cause treatment failure among people who are under ARV treatment. As a result of this, more people will be dying of AIDS related diseases. This clearly shows that drug resistance has an impact on the dynamics of HIV/AIDS transmission.

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