Bioinformatics, Proteomics and Immaging Analysis

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Research Article Open Access

Mathematical Analysis of Dual-Infection: HIV and TB Perspetive

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Abstract

A non-linear deterministic mathematical model of HIV-TB co-epidemic is formulated and analyzed. The aim of the study is to investigate the effects of dual-infection on the transmission dynamics of the two diseases. We make distinction between two processes of transmission: co-infection and super-infection. We employ traditional analytical methods of analysis to determine conditions for existence of steady states and their stability. Furthermore, we determine the reproduction number of the model using the next generation operator technique and show that the disease-free equilibrium is locally and globally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. These results have implications on the design of control strategies.

Received Date: December 9, 2015
Accepted Date: November 1, 2016
Published Date: November 8, 2016

Citation: Gosalamang Ricardo Kelatlhegile. Mathematical analysis of dual-infection: HIV and TB perspective (2016) Bioinfo Proteom Img Anal 2(2): 135- 139.

DOI: 10.15436/2381-0793.16.017

Introduction

Dual infection is infection with strains or pathogens derived from two different individuals, and can be categorized into co-infection and super-infection[1]. Co-infection is defined as an infection with two heterologous strains or pathogens either simultaneously or within a brief period of time before an infection with the first strain or pathogen has been established and an immune response has developed[2]. In the case of HIV, co-infection would occur within the first month of infection. Super-infection is defined as infection with a second strain after the initial infection and the immune response to it has been established.

Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) co-infections present an immense burden on health care systems and pose diagnostic and therapeutic challenges globally particularly in sub-Saharan Africa and Asia[2]. The two diseases interfere and impact the pathogenesis of each other, leading to a typical presentations and diagnostic complications[3,4]. These challenges have serious implications on the design, quality and continuity of care, monitoring and interpretation of control targets[5,6].

A number of mathematical models on co-infection have been formulated and analysed[7,8,9,10,11,12,13,14,15,16,17]. The studies discussed the HIV-TB associated morbidity and mortality complications and ignored a possibility of simultaneous transmission of both HIV and TB pathogens (co-infection). For instance, Sharomi et. al formulated a deterministic model of TB and HIV co-infection with the aim of evaluating the impact of various treatment strategies in reducing the burden of the twin-epidemic. Corbett et.al reviewed TB epidemiology in Africa and policy implications of HIV/AIDS treatment scale-up. The study further investigated the dynamics of drug resistance and the effects of latent co-infection on intervention that targeted latent class. Long et.al developed a co-epidemic model to study the transmission dynamics of HIV/AIDS and TB. Castillo-Chavez[18] and Song provided a detailed review transmission dynamics and control of TB. Colijn et.al developed a simple model of an infectious disease which incorporated a latent phase and compared and contrasted results of super-infection and co-infection models. In this paper, we employ the idea introduced in[19] to extend Long et.al co-infection model at population level by incorporating dual infection (co-infection and super-infection). The aim of the study is to investigate the effects of simultaneous transmission of both HIV and TB pathogens on the disease dynamics.

This paper is organized as follows: section 2, presents model formulation, model analysis is carried sections 3 (reproduction numbers, existence of equilibria) and 4 (stability analysis). In section 5, we perform some numerical analysis, and discuss and conclude the paper in section 6.

Model formulation

We consider an SII x SI x SII problem in which the host

population is divided into four mutually disconnected classes. The susceptible class, J_S, comprising individuals at risk of either HIV or TB or both (dual infection). TB-only infectious class, J_T, HIV-only infectious class, J_I, HIV-TB co-infected class, J_{IT}.

The susceptible population is replenished through births at constant recruitment rate and is decrease through infection with TB, HIV and HIV-TB infection at rates λ_I, λ_T and λ_{IT} respectively. The TB, HIV and HIV-TB co-infection compartments are replenished through infection at rates λ_I, λ_T and λ_{IT} given by

$$\lambda_I = \beta_I (J_I + \eta_I J_{IT}),\ \lambda_T = \beta_I (J_T + \eta_T J_{IT}),\ \text{and}\ \lambda_{IT} = \beta_{IT} \min(J_I, J_T)$$

Where $\beta_I \beta_T$ and $\beta_{IT} = \kappa \beta_I \beta_T$ are respectively the transmission coefficients for HIV, TB and HIV-TB. The parameter $\kappa << 1$, correspond to the assumption that the two pathogens are rarely transmitted simultaneously, while $\kappa > 1$ assumes high transmissibility of both pathogens. The modification parameters $\eta_I \geq 1$ and $\eta_T \geq 1$ account for the assumption that dually-infected individuals have higher transmission rates of HIV and TB respectively, compared to singly-infected individuals. Furthermore, the parameters $\varphi_I \geq 1$ and $\varphi_T \geq 1$ (also modification parameters) account for the level of risk of singly-infected individuals to another infection (super-infection). The host population is subjected to constant natural mortality rate μ with TB, HIV and HIV-TB populations subjected to an additional death associated to infections δ_I, δ_T and δ_{IT} respectively. Even though HIV does not cause death, we assume that individuals acquire opportunistic infections that lead to death. The description and assumptions above lead to the following autonomous system of differential equations:

$$\begin{aligned}
j_S &= \Lambda - \lambda_I J_S - \lambda_T J_S - \lambda_{IT} J_S - \mu J_S \\
j_I &= \lambda_I J_S - \varphi_I \lambda_T J_I - (\mu + \delta_I) J_I \\
j_T &= \lambda_T J_S - \varphi_I \lambda_T J_T - (\mu + \delta_T) \\
j_{IT} &= \lambda_{IT} + \varphi_T \lambda_T J_I + \varphi_I \lambda_T J_T - (\mu + \delta_{IT}) J_{IT} \quad (1)
\end{aligned}$$

with changes in the total population governed by

$\dot{N}(t) = \Lambda - \mu N - \delta_I J_I - \delta_T J_T - \delta_{IT} J_{IT}$,

Where $N(t) = J_S + J_I + J_T + J_{IT}$

Positivity of solutions and Invariant region

From equation (2), we have

$\dot{N}(t) = \Lambda - \mu N$.

which upon integration yields

$N(t) \leq 1/\mu\ [\Lambda - Ae^{-\mu t}]$. (3)

Taking the limit as t approaches infinity, we obtain

$$\limsup_{t \to \infty} N(t) \leq \frac{\Lambda}{\mu}.$$

Thus, the model represented by (1) can be analysed in the feasible region

$$\Omega = \{ (J_S + J_I + J_T + J_{IT}) \in \Re_+^4 : N(t) \leq \frac{\Lambda}{\mu} \}$$

result can be summarized with the following lemma.

Lemma 2.1

All solutions of the system (1) starting in $\Re_+^4$ are bounded and consequently enter the attracting set Ω within the first octant.

Model analysis

The model reproduction number, R_0

The basic reproduction number R_0 is defined as the number of secondary infections produced by a single infectious individual introduced in a wholly susceptible population during his or her entire infectious period[20,21]. This quantity plays a pivotal role in characterizing the epidemic and the design of control programs. Using the next generation operator by[20,21], we have decompose system (1) into a matrix of generation of new infections and other transitions as,

$$\dot{x} = F - V$$

$$= \begin{pmatrix} \lambda_I J_S \\ \lambda_T J_S \\ \varphi_T \lambda_T J_I + \varphi_I \lambda_I J_T + \lambda_{IT} J_S \\ 0 \end{pmatrix} - \begin{pmatrix} (\mu + \delta_I) J_I + \varphi_T \lambda_T J_I \\ (\mu + \delta_T) J_T + \varphi_I \lambda_I J_T \\ (\mu + \delta_{IT}) J_{IT} \\ (\lambda_I + \lambda_T + \lambda_{IT} + \mu) J_S - \Lambda \end{pmatrix} \quad (4)$$

Noting that the infected classes are J_I, J_T and J_{IT} (m = 3), we evaluate the derivatives of F and V at the disease-free equilibrium to get

$$F = \begin{pmatrix} \beta_I J_{S_0} & 0 & \eta_I \beta_I J_{S_0} \\ 0 & \beta_T J_{S_0} & \eta_T \beta_T J_{S_0} \\ 0 & 0 & \beta_{IT} J_{S_0} \end{pmatrix} \text{ and } V = \begin{pmatrix} \mu + \delta_I & 0 & 0 \\ 0 & \mu + \delta_T & 0 \\ 0 & 0 & \mu + \delta_{IT} \end{pmatrix}$$

From which, we obtain FV^{-1} and compute the reproduction number of the model, as the spectral radius or the dominant Eigen value given by

$\rho(FV^{-1}) = R_0 = \{R_{0I}, R_{0T}, R_{0IT}\}$,

Where

$R_{0I} = (\Lambda/\mu)(\beta_I/\mu + \delta_I)$, $R_{0T} = (\Lambda/\mu)(\beta_T/\mu + \delta_T)$ and $R_{0IT} = (\Lambda/\mu)(\beta_{IT}/\mu + \delta_{IT})$.

The threshold parameters R_{0I}, R_{0T} and R_{0IT} are defined as the basic reproduction numbers due to HIV, TB and HIV-TB respectively.

Theorem 3.1 *The disease-free equilibrium, E_0 is locally asymptotically stable when $R_0 < 1$ and unstable whenever $R_0 > 1$.*

To illustrate Theorem 3.1, we line arise of system (1) around the disease-free equilibrium and obtain

$$J_{E_0} = \begin{pmatrix} -\mu & -\beta_I J_{S_0} & -\beta_T J_{S_0} & -(\eta_T \beta_T + \eta_I \beta_I + \beta_{IT}) J_{S_0} \\ 0 & \beta_I J_{S_0} - \mu - \delta_I & 0 & \eta_I \beta_I J_{S_0} \\ 0 & 0 & \beta_T J_{S_0} - \mu - \delta_T & \eta_T \beta_T J_{S_0} \\ 0 & 0 & 0 & \beta_{IT} J_{S_0} - \mu - \delta_{IT} \end{pmatrix} \quad (5)$$

The eigen values of the Jacobian matrix J_{E0} are $\lambda_1 = -\mu$, $\lambda_2 = -(\mu + \delta_I)(1 - R_{0I})$, $\lambda_3 = -(\mu + \delta_T)(1 - R_{0T})$ and $\lambda_4 = -(\mu + \delta_{IT})(1 - R_{0IT})$. All eigen values λ_1, λ_2, λ_3 and λ_4 have negative real parts only if $R_{0I} < 1$, $R_{0T} < 1$ and $R_{0IT} < 1$. Thus, establishing Theorem 3.1.

Steady State solution

To determine the equilibria of system (1) we set the right hand side of the system to zero and obtain in terms of λ^*_I, λ^*_T and λ^*_{IT}.

$$J_S^* = \frac{\Lambda}{\mu + \lambda_S^* + \lambda_T^* + \lambda_{IT}^*}, \quad J_I^* = \frac{\Lambda J_S^*}{\mu + \delta_I + \varphi_T \lambda_T^*}, \quad J_T^* = \frac{\Lambda J_S^*}{\mu + \delta_T + \varphi_I \lambda_I^*}$$

$$J_{IT}^* = \left[\frac{\varphi_T \lambda_T^* \lambda_I^*}{\mu + \varphi_T \lambda_T^*} + \frac{\varphi_I \lambda_I^* \lambda_T^*}{\mu + \delta_T + \varphi_I \lambda_I^*} \right] \frac{J_S^*}{\Phi_0} \qquad (6)$$

Where $\Phi_0 = (\mu + \delta_{IT})(1 - R_{IT} J^*_S)$ and $R_{IT} = \beta_{IT} / \mu + \delta_{IT}$. We observe that the existence of equilibria is governed by the condition $R_{IT} J^*_S < 1$. The threshold parameter R_{IT} is define as the average number of new co-infections generated by a co-infected individual introduced in a wholly susceptible population.

Substituting J^*_S, J^*_I, J^*_T and J^*_{IT} into the expressions for λ_I, λ_T, and λ_{IT}, we obtain

$$\lambda_I^* = \beta_I \left[\frac{1}{\mu + \delta_I + \varphi_T \lambda_T^*} + \frac{\eta_I}{\Phi_0} \left(\frac{\varphi_T \lambda_T^*}{B_1} + \frac{\varphi_I \lambda_T}{B_2} \right) \right] \lambda_I J_S^* \qquad (7)$$

$$\lambda_T^* = \beta_T \left[\frac{1}{\mu + \delta_T + \varphi_I \lambda_I^*} + \frac{\eta_I}{\Phi_0} \left(\frac{\varphi_T \lambda_I^*}{B_1} + \frac{\varphi_I \lambda_I}{B_2} \right) \right] \lambda_T J_S^* \qquad (8)$$

$$\lambda_T^* = \left(\frac{R_{IT}^I}{1 + \hat{\varphi}_T \lambda_T^*} + \frac{R_{IT}^T}{1 + \hat{\varphi}_I \lambda_I^*} \right) \left(\frac{J_S^*}{\mu + \delta_{IT}} \right) \left(\frac{\lambda_I^* \lambda_T^*}{1 - R_{IT} J_S^*} \right) \qquad (9)$$

Where $\varphi_T = \varphi_T / \mu + \delta_I$, $\varphi_I = \varphi_I / \mu + \delta_I$, $B_1 = \mu + \varphi_I \lambda^*_T$ and $B_2 = \mu + \varphi_I \lambda^*_I$, $R_{IT}^I = \frac{\varphi_T \beta_{IT}}{\mu + \delta_I}$ and $R_{IT}^T = \frac{\varphi_I \beta_{IT}}{\mu + \delta_T}$

The threshold parameters R_{IT}^I is defined as the average number of new dual infections due to an HIV infective introduced into a TB infected population, while and R_{IT}^T is the average number of new dual infections due to a TB infective introduced in an HIV infected population.

The solutions (7) and (8) lead to the following results

$\lambda^*_I = 0$ or $F_1(\lambda^*_I, \lambda^*_T) = 1$ and $\lambda^*_I = 0$ or $F_2(\lambda^*_I, \lambda^*_T) = 1$, (10)

With

$$F_1 = \beta_I \left[\frac{1}{\mu + \delta_I + \varphi_T \lambda_T^*} + \frac{\eta_I}{\Phi_0} \left(\frac{\varphi_T \lambda_T^*}{B_1} + \frac{\varphi_I \lambda_T}{B_2} \right) \right] \lambda_I J_S^*$$

$$F_2 = \beta_T \left[\frac{1}{\mu + \delta_T + \varphi_I \lambda_I^*} + \frac{\eta_I}{\Phi_0} \left(\frac{\varphi_T \lambda_I^*}{B_1} + \frac{\varphi_I \lambda_I}{B_2} \right) \right] \lambda_T J_S^* \quad (11)$$

Due to non-linearity of the pair of equations (11), it is not easy to obtain the analytical solution for the interior equilibrium point resulting from the intersection of F_1 and F_2. However, numerically we were able to demonstrate existence and non-existence of the interior point (results not included).

Disease-free equilibrium point

The solutions $\lambda^*_I = 0$ and $\lambda^*_T = 0$, in results (10) lead to the disease-free equilibrium given by

$E_0 = (\Lambda / \mu, 0,0,0)$.

TB-state

The case $\lambda^*_I = 0$ and $\lambda^*_T \neq 0$, lead to the TB-state given by

$$E_T = \left(\frac{\Lambda}{\mu R_{0T}}, 0, \frac{\Lambda (R_{0T} - 1)}{(\mu + \delta_T) R_{0T}}, 0 \right)$$

Where $R_{0T} = \left(\frac{\Lambda}{\mu} \right) \left(\frac{\beta_T}{\mu + \delta_T} \right) > 0$.

HIV-state

The case $\lambda^*_I \neq 0$ and $\lambda^*_T = 0$, lead to the HIV-state given by

$$E_I = \left(\frac{\Lambda}{\mu R_{0T}}, \frac{\Lambda (R_{0I} - 1)}{(\mu + \delta_I) R_{0I}}, 0, 0 \right)$$

Where $R_{0I} = \left(\frac{\Lambda}{\mu} \right) \left(\frac{\beta_I}{\mu + \delta_I} \right) > 0$.

Dual infection (full model)

The full dual infection model is complex to obtain solutions in compact form. Simple numerical simulations are carried out in section 5, to provide insight in the transmission dynamics of dual infection.

Global stability

Theorem 4.1: *The disease-free equilibrium of the HIV and TB dual-infection model (1), is globally asymptotically stable whenever $R_0 < 1$ and unstable when $R_0 > 1$.*

We construct a Lyapunov function of the form

$V(J_S, J_I, J_T, J_{IT}) = J_S - J_{S0} - J_{S0} \ln(J_S / J_{S0}) + J_I + J_T + J_{IT}$.

The time derivative of $V(J_S, J_I, J_T, J_{IT})$ along the solution path yields

$dV/dt = \Lambda - \lambda_I J_S - \lambda_T J_S - \lambda_{IT} J_S - J_{S0} / J_S (\Lambda - \lambda_I J_S - \lambda_T J_S - \lambda_{IT} J_S) + \lambda_I J_S - \varphi_T \lambda_T J_I - (\mu + \delta_I) J_I + \lambda_T J_S - \varphi_I \lambda_I J_T - (\mu + \delta_T) J_T + \varphi_T \lambda_T J_I + \varphi_I \lambda_I J_T + \lambda_{IT} J_S - (\mu + \delta_{IT}) J_{IT}$

Evaluating the time derivative at the disease-free equilibrium level and we obtain

$dV/dt = \mu J_{S0} - \mu J_S - J_{S0} / J_S (\mu J_{S0} - \lambda_I J_S - \lambda_T J_S - \lambda_{IT} J_S) - (\mu + \delta_I) J_I - (\mu + \delta_T) J_T - (\mu + \delta_{IT}) J_{IT}$,

$= - \{ \mu (J_S - J_{S0} / J_S) + \kappa (\mu + \delta_T)(1 - R_{0T}) \} - \{ \kappa \mu (1 - R_{0I}) J_I + \kappa (\mu + \delta_{IT}) (1 - R_{0IT}) J_{IT} \} \leq 0$

Provided $R_{0I} \leq 1$, $R_{0T} \leq 1$ and $R_{0IT} \leq 1$.

If $R_0 < 1$, $\dot{V} = 0$ implies $J_I = 0$, $J_T = 0$ and $J_{IT} = 0$. It follows from system (1) that the largest invariant set where $\dot{V} = 0$ satisfies $J_I = 0$, $J_T = 0$, $J_{IT} = 0$, and $J_S = \Lambda / \mu = J_{S0}$. By Lassalle's invariance principle[22], the disease-free equilibrium is globally asymptotically stable.

Numerical simulation

In this section, we present numerical results to illustrate analytical results and to demonstrate results which could not be solved analytically, using published data from literature. We consider various scenarios to assess the impact of the infectivity rates in the transmission dynamics of the co-epidemic. The following parameter values are used in the simulations (Table 1).

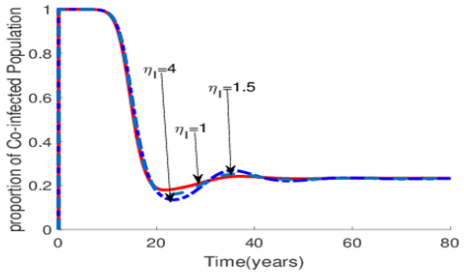
We consider five key modification parameters associated with co-infection ($\eta_I \eta_T \kappa$) and super-infection (φ_I, φ_T). We wish to address the question ``How does levels of infectivity of co-infected individuals affect the dynamics of HIV and TB epidemics?

Figures 1(a) and 1(b) present variation in the magnitudes of η_I. Increasing the values of η_T we obtain drastic increase in the prevalence of HIV to maximum levels and settle at different levels. The results show marked increase in HIV-TB co-infection prevalence, that remain for some time at high levels before reducing drastically to low levels and settle at a common endemic state.

Table 1: parameter values for simulation.

Parameters	Units	Values	Citation
Λ	People/year	0.29	[1]
δ_{IT}	/year	0.5	[1]
δ_I	/year	0.025	[21]
δ_T	/year	0.01	[21]
β_I	-	0.5586	[6]
β_T	-	0.31025	[6]
η_I	-	1 - 4	[10]
η_T	-	1 - 1.6	[21]
φ_I	-	1 - 4	Varied
φ_T	-	1 - 4	Varied
μ	/year	0.02	[21]
κ	-	1 - 10	Varied

Increasing η_T (Figures 2(a) and 2(b)) on the other hand rapidly increases the prevalence of TB to the maximum level before reducing and settling at low levels. The prevalence of HIV-TB drastically increases and settles at high levels for some time before drastically reducing and settling at low levels.



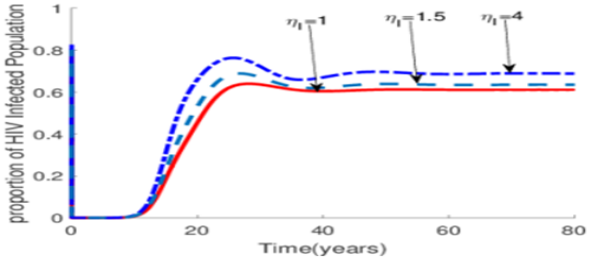
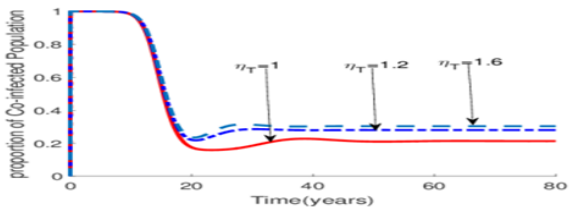


Figure 1: Variation of η_I with all other parameters fixed.
$\Lambda = 0{,}29$, $\delta_{IT} = 0{,}5$, $\beta_I = 0{,}5586$, $\beta_T = 0{,}31025$, $\delta_T = 0{,}03$, $\delta_T = 0{,}02$, $\delta_I = 0.01$, $\beta_{IT} = 0{,}6$, $\varphi_I = 1{,}1$, $\varphi_T = 1{,}03$.



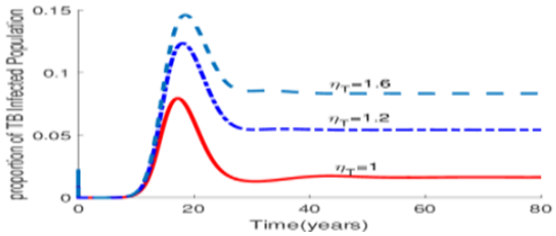
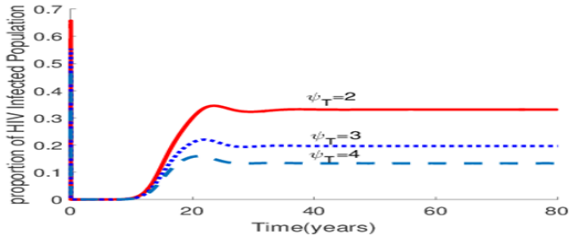


Figure 2: Variation of with all other parameters fixed.
$\Lambda = 0{,}29$, $\delta_{IT} = 0{,}5$, $\beta_I = 0{,}5586$, $\beta_T = 0{,}31025$, $\delta_T = 0{,}03$, $\delta_T = 0{,}02$, $\delta_I = 0.01$, $\beta_{IT} = 0{,}6$, $\varphi_I = 1{,}1$, $\varphi_T = 1{,}03$.



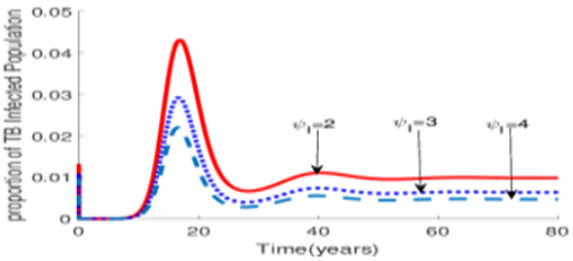


Figure 3: (a) Variation of and (b) variation of with all other parameters fixed.
$\Lambda = 0{,}29$, $\delta_{IT} = 0{,}5$, $\beta_I = 0{,}5586$, $\beta_T = 0{,}31025$, $\delta_T = 0{,}03$, $\delta_T = 0{,}02$, $\delta_I = 0.01$, $\beta_{IT} = 0{,}6$, $\varphi_I = 1{,}1$, $\varphi_T = 1{,}03$.

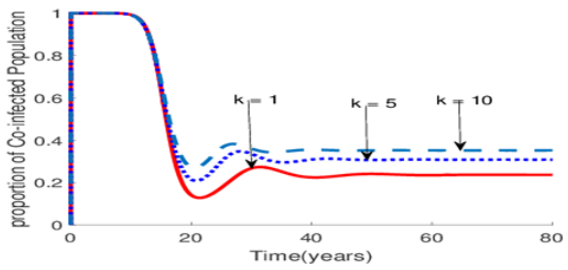


Figure 4: Variation of k to assess effects of simultaneous transmission of two pathogens.

These results confirm findings from other studies which indicate that the two pathogens exhibit a synergistic relationship that is, each pathogen exacerbates the progression of the other[16,23,24]. Increase effects on super-infection such as increased risk of TB infectives to HIV φ_I or increased risk of HIV infectives to TB φ_T has the effect of reducing the prevalence of singly-infected populations and increasing the dually infected population (Figures 3(a) and 3(b)). The suggests that the dual infection prevalence is not sensitive to increased effects in simultaneous transmission of pathogens (Figure 4).

Discussion

A non-linear deterministic mathematical model of dual infection of HIV and TB is formulated and analysed. The aim of the study is to investigate the effects of simultaneous transmission of both HIV and TB pathogens on the disease dynamics. We assume a possibility of simultaneous transmission of both HIV and TB pathogens to susceptible individuals. We employ traditional analytical method of analysis to determine the steady states and their stability. The study showed that the disease-free equilibrium exists for all values of the reproduction number R_0 and is locally and globally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. Numerical simulations were used to confirm analytical results. Analytically, we determined additional threshold parameters which govern super-infection. Our model was highly simplified but still led to a complex and very difficult problem to solve analytically. The symmetry of solution equations seem to suggest that techniques in advanced linear algebra (co-planar systems) or advanced vector calculus may provide insights conditions for existence of the interior solution (co-existence). Further studies are required to systematically compute the reproduction number for super-infection.

Acknowledgement: The authors are grateful to anonymous referees and the managing editor for having read the paper and for their valuable comments, which constitute to the betterment of the manuscript.

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