Mathematical Analysis of Dual-Infection: HIV and TB Perspective

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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.

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[3]. 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, \( S \), comprising individuals at risk of either HIV or TB or both (dual infection), TB-only infectious class, \( I_T \), HIV-only infectious class, \( I_H \), 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 \( \lambda_I \), \( \lambda_H \) and \( \lambda_{IT} \) respectively. The TB, HIV and HIV-TB co-infection compartments are replenished through infection at rates \( \lambda_I \), \( \lambda_H \) and \( \lambda_{IT} \), given by

\[
\lambda_I = \beta_I (J_T + \eta_I J_H), \quad \lambda_H = \beta_H (J_T + \eta_H J_H), \quad \text{and} \quad \lambda_{IT} = \beta_{IT} \min(J_I, J_T)
\]

Where \( \beta_I \) and \( \beta_H \) are the transmission coefficients, \( \eta_I \) and \( \eta_H \) are modification parameters which 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 \( \mu \) with TB, HIV and HIV-TB populations subjected to an additional death associated to infections \( \delta_I \), \( \delta_H \) and \( \delta_{IT} \) 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:

\[
\begin{align*}
J_T' &= -\lambda_I J_T - \lambda_H J_H - \lambda_{IT} J_{IT} + \mu J_T - \mu S_T - \delta J_T \\
J_H' &= -\lambda_I J_T - \lambda_H J_H - \lambda_{IT} J_{IT} + \mu J_H - \mu S_H - \delta J_H \\
J_{IT}' &= -\lambda_I J_T - \lambda_H J_H - \lambda_{IT} J_{IT} + \mu J_{IT} - \mu S_{IT} - \delta J_{IT}
\end{align*}
\]

with changes in the total population governed by

\[
\begin{align*}
N(t) &= \Lambda - \mu N - \delta J_T - \delta J_H - \delta J_{IT} \\
N(t) &= J_T + J_H + J_{IT}
\end{align*}
\]

**Positivity of solutions and Invariant region**

From equation (2), we have

\[
\dot{N}(t) = \Lambda - \mu N
\]

which upon integration yields

\[
N(t) \leq \frac{\Lambda}{\mu} \left[ 1 - e^{-\mu t} \right].
\]  

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

\[
\Omega = \{ J_T + J_H + J_{IT} + J_H \} \in \mathbb{R}^4 \setminus \{ N(t) \leq \frac{\Lambda}{\mu} \}
\]

result can be summarized with the following lemma.

**Lemma 2.1**

All solutions of the system (1) starting in \( \Omega \) are bounded and consequently enter the attracting set \( \Omega \) within the first octant.

**Model analysis**

The model reproduction number, \( R_0 \)

\[
\dot{x} = F - V
\]

Where \( \dot{x} = \begin{pmatrix} J_T' \\ J_H' \\ J_{IT}' \\ 0 \end{pmatrix} \), \( F = \begin{pmatrix} \begin{pmatrix} \lambda_I J_T + \lambda_H J_H + \lambda_{IT} J_{IT} - \mu J_T \\ \lambda_I J_T + \lambda_H J_H + \lambda_{IT} J_{IT} - \mu J_H \\ \lambda_I J_T + \lambda_H J_H + \lambda_{IT} J_{IT} - \mu J_{IT} \\ 0 \end{pmatrix} \end{pmatrix} \) and \( V = \begin{pmatrix} \begin{pmatrix} \mu + \delta_T \end{pmatrix} J_T + \phi_J J_T \\ \mu + \delta_H J_H + \phi_J J_H \\ \mu + \delta_{IT} J_{IT} + \phi_J J_{IT} \\ 0 \end{pmatrix} \)

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,

\[
E = \begin{pmatrix} \lambda_I J_T + \lambda_H J_H + \lambda_{IT} J_{IT} - \mu J_T \\ \lambda_I J_T + \lambda_H J_H + \lambda_{IT} J_{IT} - \mu J_H \\ \lambda_I J_T + \lambda_H J_H + \lambda_{IT} J_{IT} - \mu J_{IT} \\ 0 \end{pmatrix}
\]

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

\[
F = \begin{pmatrix} \mu J_{IT} \\ \mu J_{IT} \\ \mu J_{IT} \\ 0 \end{pmatrix}
\]

\[
V = \begin{pmatrix} \mu + \delta_T \\ \mu + \delta_H \\ \mu + \delta_{IT} \\ 0 \end{pmatrix}
\]

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

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

Where \( R_{0T} = (\Lambda/\mu)(\beta_I/\mu + \delta_T) \), \( R_{0I} = (\Lambda/\mu)(\beta_I/\mu + \delta_I) \) 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

\[
J_{IT} = \begin{pmatrix} -\mu & -\beta_I J_T & -\beta_H J_H & -\beta_{IT} J_{IT} \\ 0 & \beta_I J_T - \mu - \delta_T & 0 & 0 \\ 0 & 0 & \beta_H J_H - \mu - \delta_T & 0 \\ 0 & 0 & 0 & \beta_{IT} J_{IT} - \mu - \delta_{IT} \end{pmatrix}
\]

The eigen values of the Jacobian matrix \( J_{IT} \) are \( \lambda_1 = -\mu, \lambda_2 = -(-\mu + \delta_T)(1 - R_{0T}), \lambda_3 = -(-\mu + \delta_H)(1 - R_{0I}) \) and \( \lambda_4 = -(-\mu + \delta_{IT})(1 - R_{0IT}) \). All eigen values \( \lambda_1, \lambda_2, \lambda_3, \lambda_4 \) have negative real parts only if \( R_{0T} < 1, R_{0I} < 1 \) and \( R_{0IT} < 1 \). Thus, establishing Theorem 3.1.
\[ J'_z = \frac{\Lambda}{\mu + \delta_T + \phi_T \lambda_T}, \quad J'_r = \frac{\Lambda J'_z}{\mu + \delta_T + \phi_T \lambda_T}, \quad J'_p = \frac{\Lambda J'_z}{\mu + \delta_T + \phi_T \lambda_T} \]

\[ J'_r = \left[ \frac{\phi_T \lambda_T^2 \lambda_T'}{\mu + \phi_T \lambda_T'} + \frac{\phi_T \lambda_T^2 \lambda_T'}{\mu + \phi_T \lambda_T'} \right] \frac{J'_z}{\Phi_0} \]

Where \( \Phi_0 = (\mu + \delta_T)(1 - R_{IT}) \) and \( R_{IT} = \beta_{IT} / (\mu + \delta_T) \). We observe that the existence of equilibria is governed by the condition \( R_{IT} < 1 \). The threshold parameter \( R_{IT} \) is defined as the average number of new co-infections generated by a co-infected individual introduced in a wholly susceptible population. Substituting \( J'_z, J'_r, J'_T \) and \( J'_p \) into the expressions for \( \lambda'_z, \lambda'_r, \lambda'_T \) and \( \lambda'_p \), we obtain

\[ \lambda'_z = \beta_z \left( \frac{1}{\mu + \delta_T + \phi_T \lambda_T} + \frac{\eta_z}{\Phi_0} \left( \frac{\phi_T \lambda_T^2}{B_z} + \frac{\phi_T \lambda_T^2}{B_z} \right) \right) \lambda_T J'_z \]

\[ \lambda'_r = \beta_r \left( \frac{1}{\mu + \delta_T + \phi_T \lambda_T} + \frac{\eta_r}{\Phi_0} \left( \frac{\phi_T \lambda_T^2}{B_r} + \frac{\phi_T \lambda_T^2}{B_r} \right) \right) \lambda_T J'_z \]

\[ \lambda'_p = \left( \frac{R_{IT}'}{1 + \phi_T \lambda_T'} + \frac{R_{IT}'}{1 + \phi_T \lambda_T'} \right) \left( \frac{J'_z}{\mu + \delta_T} \right) \lambda_T J'_z \]

Where \( \phi_T = \phi_T / (\mu + \delta_T) \), \( \eta_z = \phi_T / (\mu + \delta_T) \), \( B_z = \mu + \phi_T \lambda_T \), and \( B_R = \mu + \phi_T \lambda_T \).

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

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

\[ \lambda'_z = 0 \text{ or } F_1(\lambda'_z, \lambda'_r) = 1 \quad \text{and} \quad \lambda'_r = 0 \text{ or } F_2(\lambda'_z, \lambda'_r) = 1 \]

With

\[ F_1 = \beta_z \left( \frac{1}{\mu + \delta_T + \phi_T \lambda_T} + \frac{\eta_z}{\Phi_0} \left( \frac{\phi_T \lambda_T^2}{B_z} + \frac{\phi_T \lambda_T^2}{B_z} \right) \right) \lambda_T J'_z \]

\[ F_2 = \beta_r \left( \frac{1}{\mu + \delta_T + \phi_T \lambda_T} + \frac{\eta_r}{\Phi_0} \left( \frac{\phi_T \lambda_T^2}{B_r} + \frac{\phi_T \lambda_T^2}{B_r} \right) \right) \lambda_T J'_z \]

Due to non-linearity of the pair of equations (11), it is not easy to obtain the analytical solution for the interior equilibrium result 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 \( \lambda'_z = 0 \) and \( \lambda'_r = 0 \), in results (10) lead to the disease-free equilibrium given by

\[ E_0 = (\Lambda / (\mu, 0, 0, 0)) \]

**TB-state**

The case \( \lambda'_z = 0 \) and \( \lambda'_r \neq 0 \), lead to the TB-state given by

\[ E_T = \left( \frac{\Lambda}{\mu R_{IT}}, 0, \frac{\Lambda (R_{IT} - 1)}{(\mu + \delta_T) R_{IT}}, 0 \right) \]

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

**HIV-state**

The case \( \lambda'_z \neq 0 \) and \( \lambda'_r = 0 \), lead to the HIV-state given by

\[ E_I = \left( \frac{\Lambda}{\mu R_{IT}}, \frac{\Lambda (R_{IT} - 1)}{(\mu + \delta_T) R_{IT}}, 0, 0 \right) \]

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

**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

\[ V(J_S, J_I, J_T, J_R) = J_S - J_{S0} - \ln(J_S / J_{S0}) + J_I + J_T + J_R \]

The time derivative of \( V(J_S, J_I, J_T, J_R) \) along the solution path yields

\[ \frac{dV}{dt} = \Lambda - \lambda J_S - \lambda J_T - \lambda J_I - \lambda J_R - J_S / \lambda (\Lambda - \lambda J_S - \lambda J_T - \lambda J_I - \lambda J_R) \]

\[ + \lambda J_S \varphi J_T - (\mu + \delta_J) (J_T + \lambda J_S - \lambda J_T - \lambda J_I - \lambda J_R) \]

\[ + \lambda J_T \varphi \delta J_I - (\mu + \delta_J) (J_I + \lambda J_S - \lambda J_T - \lambda J_I - \lambda J_R) \]

\[ + \phi J_T \delta J_I + \phi J_T \delta J_I - (\mu + \delta_J) J_T \]

\[ = - \{J_S (J_S - J_{S0}) + \kappa (\mu + \delta_J) (1 - R_{IT}) - \kappa \mu (1 - R_{IT}) J_T + \kappa (\mu + \delta_J) \}

\[ (1 - R_{IT}) J_T \] 0 \]

Provided \( R_{IT} < 1, R_{IT} < 1 \) and \( R_{IT} < 1 \).

If \( R_0 < 1, \dot{V} = 0 \) implies \( J_S = 0, J_I = 0 \) and \( J_T = 0 \). It follows from system (1) that the largest invariant set where \( \dot{V} = 0 \) satisfies \( J_S = 0, J_I = 0, J_T = 0, \) and \( J_R = \Lambda / (\mu) \). By Lassalle's invariance principle\(^{[21]} \), 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 ($\phi_I, \phi_T$). 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 $\eta_I$. Increasing the values of $\eta_T$ 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.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Units</th>
<th>Values</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Lambda$</td>
<td>People/year</td>
<td>0.29</td>
<td>[1]</td>
</tr>
<tr>
<td>$\delta_{IT}$</td>
<td>/year</td>
<td>0.5</td>
<td>[1]</td>
</tr>
<tr>
<td>$\delta_T$</td>
<td>/year</td>
<td>0.025</td>
<td>[21]</td>
</tr>
<tr>
<td>$\delta_I$</td>
<td>/year</td>
<td>0.01</td>
<td>[21]</td>
</tr>
<tr>
<td>$\beta_I$</td>
<td>-</td>
<td>0.5586</td>
<td>[6]</td>
</tr>
<tr>
<td>$\beta_T$</td>
<td>-</td>
<td>0.31025</td>
<td>[6]</td>
</tr>
<tr>
<td>$\eta_I$</td>
<td>-</td>
<td>1 - 4</td>
<td>[10]</td>
</tr>
<tr>
<td>$\eta_T$</td>
<td>-</td>
<td>1 - 1.6</td>
<td>[21]</td>
</tr>
<tr>
<td>$\phi_I$</td>
<td>-</td>
<td>1 - 4</td>
<td>Varied</td>
</tr>
<tr>
<td>$\phi_T$</td>
<td>-</td>
<td>1 - 4</td>
<td>Varied</td>
</tr>
<tr>
<td>$\mu$</td>
<td>/year</td>
<td>0.02</td>
<td>[21]</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>-</td>
<td>1 - 10</td>
<td>Varied</td>
</tr>
</tbody>
</table>

Increasing $\eta_T$ (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 2: Variation of $\eta_T$ with all other parameters fixed. $\Lambda = 0.29, \delta_{IT} = 0.5, \beta_I = 0.5586, \beta_T = 0.31025, \delta_I = 0.03, \delta_T = 0.02, \delta_I = 0.01, \beta_{IT} = 0.6, \phi_T = 1.1, \phi_I = 1.03$.

Figure 3: (a) Variation of $\eta_I$ and (b) variation of $\eta_T$ with all other parameters fixed. $\Lambda = 0.29, \delta_{IT} = 0.5, \beta_I = 0.5586, \beta_T = 0.31025, \delta_I = 0.03, \delta_T = 0.02, \delta_I = 0.01, \beta_{IT} = 0.6, \phi_T = 1.1, \phi_I = 1.03$.

Figure 1: Variation of $\eta_I$ with all other parameters fixed. $\Lambda = 0.29, \delta_{IT} = 0.5, \beta_I = 0.5586, \beta_T = 0.31025, \delta_I = 0.03, \delta_T = 0.02, \delta_I = 0.01, \beta_{IT} = 0.6, \phi_T = 1.1, \phi_I = 1.03$. 

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Mathematical analysis of dual-infection

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[16,21,24]. Increase effects on super-infection such as increased risk of TB infectives to HIV $\varphi_r$, or increased risk of HIV infectives to TB $\varphi_t$ 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 $R_0<1$. 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.

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Reference