

## MODELING THE INTERACTION BETWEEN AIDS AND TUBERCULOSIS

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**Abstract**—A deterministic model is proposed for the study of the dynamics of acquired immunodeficiency syndrome (AIDS) and tuberculosis (TB) co-infection. The model is comprised by a set of sixteen ordinary differential equations representing different states of both diseases, and it is intended to provide a theoretical framework for the study of the interaction between both infections. Numerical simulations of the model resulted in three striking outcomes: first, the pathogenicity of Human Immunodeficiency Virus (HIV) is enhanced by the presence of TB, and vice-versa; second, the prevalence of AIDS is higher in the presence of TB; and third, relative risk analysis demonstrated a much stronger influence of AIDS on TB than the other way around.

### INTRODUCTION

The steady decline in the annual number of cases of tuberculosis observed in the United States since the early fifties reversed dramatically after 1984 [1]. For instance, from 1975 through 1984, tuberculosis case rates decreased from 15.9 to 9.4 per 100 000 population, an average decline of 5.7% annually [2]. The number of cases rose by 3 percent in 1986, by 5 percent in 1989, and by more than 6 percent in 1990 [3–6]. This upheaval in the incidence of tuberculosis has been attributed to the human immunodeficiency virus epidemic [1].

Overall tuberculosis has been found to occur in 4.2 percent of patients with AIDS in the United States [7]. In Canada, studies have shown a total of 15 cases of tuberculosis among 464 AIDS patients in the period from 1983 to 1988, giving a prevalence of 3.2 percent [8]. In some American inner-city areas, blacks and Hispanics have accounted for between 80 to 100 percent of the cases of AIDS and tuberculosis [9]. Data from Florida [10] indicate a relative odds ratio of tuberculosis in patients with AIDS of 3.4, 5.5, and 10.5 when Hispanics, blacks, and Haitians, respectively, are compared with non-Hispanic whites. A recent study in New York points out the propensity of HIV infection, without AIDS-related disease, to activate remote dormant tuberculosis infection [11].

Therefore, the occurrence of tuberculosis as a sentinel infection in risk groups for HIV infection should be stressed, at least for developed countries [12].

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Infection with the human immunodeficiency virus causes a progressive and ultimately profound reduction in the cell-mediated immune response, thus setting the stage for a variety of opportunistic infections, including *Mycobacterium tuberculosis* and *avium* [13].

The interaction of HIV and tuberculosis is well-documented, and the need to understand it has been set as a priority in the global program against AIDS [14–16].

This paper has the objective of providing a theoretical framework aimed at evaluating the interaction between AIDS and tuberculosis, upon which biological realities could be taken into account, and is organized as follows: after this introduction, we present a section which describes the model's structure, assumptions, and the compartment and parameter definitions. The next section presents the equation which describe the model's dynamics. In the following section, we perform a sensibility and equilibrium analysis which is central for the determination of the transmission parameters. Presented next are the numerical simulations of the model, whose results allow an epidemiological analysis intended to quantify the interaction between both infections. The final section discusses the paper's proposals and the model's implications.

## THE MODEL

The model proposed has a structure comprised by sixteen compartments representing different states of both infections. Two basic versions can be analyzed, one representing a closed population, in the sense that the total population is taken to be constant, mimicking situations like prisons or mental institutions, and an open version, in which the total number of individuals is taken to be a dynamic variable. Since the qualitative outcomes of both versions are quite similar, in this paper, we present only the analysis of the closed one.

The model assumes a homogeneity mixing pattern of transmission for both infections. Individuals are assumed to get HIV infection by all possible manners, a fraction of whom remain so, without developing full-blown AIDS in the absence of tuberculosis. It is also assumed that AIDS patients are so ill that they are unlikely to transmit the infection. All the active tuberculosis cases are assumed to be infective. We consider reinfection by *Mycobacterium* as a possibility, although this is a rare event.

Figure 1 shows a block diagram representing the model's structure whose variables and parameters are summarized by Table 1. We consider two types of susceptible individuals, represented by  $X_1(t)$ , who are susceptible to both infections and  $X_2(t)$ , who are also susceptible to both infections but have been infected by *Mycobacterium* (TB) at least once in the past. Individuals acquire the HIV infection with a rate of  $\beta$  individuals per unit of time, and TB infection with a rate of  $\lambda$  individuals per unit of time. The parameter  $\beta$  includes implicitly, the way a particular subfraction of the susceptible population acquired the infection. So, for instance, in a case where the infection occurred via sexual contact, the average number of sexual partners is implicitly comprised by  $\beta$ . HIV-positive individuals are represented by the compartments labelled  $Z(t)$ , who remain healthy;  $Y_1(t)$ , who will develop the AIDS-Related-Complex syndrome ( $ARC_1(t)$  and ( $ARC_2(t)$ ) after the incubation period  $1/\gamma_i$  ( $i = 1, 2$ );  $Y_2(t)$ , who will develop AIDS ( $A_1(t)$  and  $A_2(t)$ ) after the incubation period  $1/\omega_i$  ( $i = 1, 2$ );  $Y_3(t)$ , who are HIV-positive and have been infected by TB at least once in the past and who will develop AIDS ( $A_3(t)$ ) after an incubation period  $1/\omega_5$ ; and  $Y_4(t)$ , who are HIV-positive and have active tuberculosis disease. The latter will develop AIDS ( $ATbc(t)$ ) after an incubation period  $1/\xi$ . Individuals in the compartment labelled  $ARC_2(t)$  develop full-blown AIDS after a period  $1/\omega_i$  ( $i = 3, 4$ ). AIDS patients in the compartment labelled  $A_1$  remain so whilst  $A_2$  patients are susceptible to tuberculosis infection, acquiring it at a rate  $\lambda$ . Patients in the compartment labelled  $A_3$  can develop tuberculosis either by reinfection, at a rate  $\lambda'''$ , or by reactivation of their primary complex, at rate  $\sigma_3$ .

Once infected by TB, all individuals but  $A_2$  and  $A_3$  pass through a transition compartment  $I_i$  ( $i = 1$  if from  $X_j$  and 2 if from  $Y_k$  ( $k = 1, 2, 3$ ),  $Z$  or  $ARC_j$  ( $j = 1, 2$ )), after which individuals either become ill or latent, with rates  $\delta_i$  and  $\rho_i$  ( $i = 1, 2$ ), respectively. Table 1 summarizes the variable and parameter definitions.

It should be pointed out that although HIV<sup>+</sup> individuals acquire TB infection with the same rate  $\lambda$  as the negative ones, they evolve to tuberculosis disease with a rate that is the double value as that for the HIV<sup>-</sup> individuals. This assumption is expressed by the ratio  $\delta_i/\rho_i$ , whose

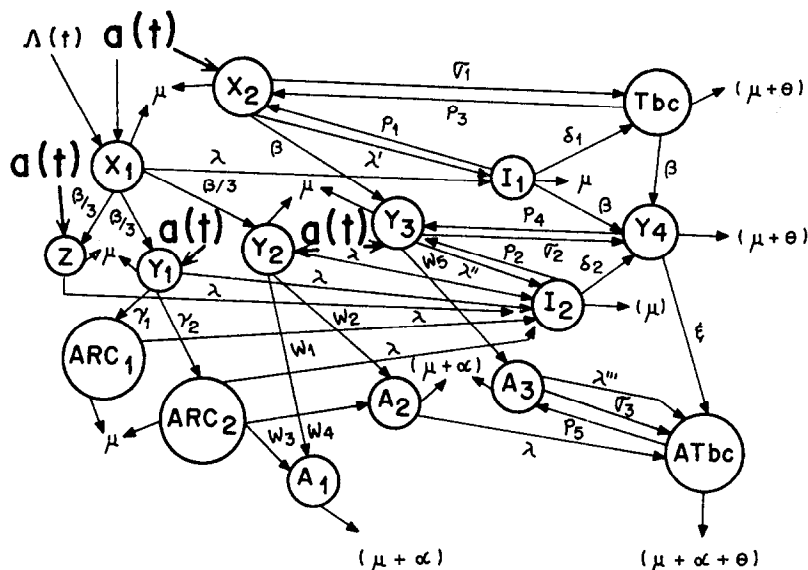


Figure 1. Flow chart representing the compartmental structure of the model.

Table 1. Variable and parameter definitions.

Parameters	Variables
$A(t)$ = immigration rate (closed version)	$X_1(t)$ = Susceptible to both infections
$\Lambda(t)$ = maternity function open version	$X_2(t)$ = Susceptible with latent tuberculosis
$\beta$ = transmission rate for HIV	$I_1(t)$ = Infected with tuberculosis
$\lambda$ = transmission rate for tuberculosis	$Z(t)$ = Healthy seropositive
$\gamma_i$ = inverse of the incubation period for ARC	$Y_{i=1,2}(t)$ = HIV-positive
$\omega_i$ = inverse of the incubation period for AIDS	$Y_3(t)$ = HIV-positive with latent tuberculosis
$\rho_i$ = recovery rate for tuberculosis infection and disease	$Y_4(t)$ = HIV-positive with active tuberculosis
$\delta_i$ = inverse of the incubation period for tuberculosis	$ARC_i(t)$ = AIDS-Related-Complex
$\sigma_i$ = reactivation of tuberculosis disease	$I_2(t)$ = HIV-positive infected with tuberculosis
$\xi$ = inverse of the incubation period for AIDS with active tuberculosis	$A_{i=1,2}(t)$ = AIDS
$\mu$ = natural mortality rate	$A_3(t)$ = AIDS with latent tuberculosis
$\alpha$ = AIDS mortality rate	$Tbc(t)$ = Active tuberculosis
$\theta$ = Tuberculosis mortality rate	$ATbc(t)$ = AIDS with active tuberculosis

values are shown in Table 2. Active cases of tuberculosis can recover spontaneously with a rate  $\rho_k$  ( $k = 3, 4, 5$ ), and the other way around, latent cases can reactivate with a rate  $\sigma_i$  ( $i = 1, 2, 3$ ). Reinfection with TB occurs with rates  $\lambda'$ ,  $\lambda''$ , and  $\lambda'''$  as we consider healthy individuals, HIV-positive, and AIDS patients, respectively.

Individuals enter into the system with a rate  $a(t)$ , meaning a birth rate for the open and an immigration rate for the closed versions of the model. Rates  $\mu$ ,  $\alpha$ , and  $\theta$  represent the natural mortality, lethality to AIDS, and lethality to tuberculosis, respectively.

Table 2. Parameters and initial condition values for the simulation of the closed model.

Parameter	Initial Condition
$\beta = 0.40$	$X_1(0) = 0.662$
$\lambda = 1.20$	$X_2(0) = 0.3$
$\lambda' = 0.0024$	$I_1(0) = 0$
$\lambda'' = 0.0048$	$Z(0) = 0.007$
$\lambda''' = 0.0096$	$Y_1(0) = 0.007$
$\gamma_1 = 0.1$	$Y_2(0) = 0.007$
$\gamma_2 = 0.23$	$Y_3(0) = 0.007$
$\omega_1 = 0.005$	$Y_4(0) = 0$
$\omega_2 = 0.1$	$ARC_1(0) = 0$
$\omega_3 = 0.11$	$ARC_2(0) = 0$
$\omega_4 = 0.22$	$A_1(0) = 0$
$\omega_5 = 0.15$	$A_2(0) = 0$
$\rho_1 = 8.0$	$A_3(0) = 0$
$\rho_2 = 6.0$	$Tbc(0) = 0.01$
$\rho_3 = 0.8$	$ATbc(0) = 0$
$\rho_4 = 0.5$	$I_2(0) = 0$
$\rho_5 = 0.2$	$a(0) = 0.0155$
$\delta_1 = 0.1$	$N(0) = 1.0$
$\delta_2 = 0.15$	
$\sigma_1 = 0.065$	
$\sigma_2 = 0.1$	
$\sigma_3 = 0.33$	
$\xi = 0.33$	
$\mu = 0.15$	
$\alpha = 0.33$	
$\theta = 0.05$	

## MODEL'S EQUATIONS

The model's dynamics are described by a system of non-linear ordinary differential equations, in which we call:

$$\text{HIV}^+ = \frac{p_1 Z(t) + p_2 [Y_1(t) + Y_2(t) + Y_3(t) + Y_4(t)] + p_3 \text{ARC}_1(t) + p_4 \text{ARC}_2(t)}{N(t)}$$

and

$$\text{TB} = \frac{p_5 [Tbc(t) + Y_4(t)] + p_6 \text{ATbc}(t)}{N(t)}$$

The set of equations has the form:

$$\frac{dX_1(t)}{dt} = a(t)X_1(0) - X_1(t) [\beta(\text{HIV}^+) + \lambda(\text{TB}) + \mu] \quad (1)$$

$$\frac{dX_2(t)}{dt} = a(t)X_2(0) + \rho_1 I_1(t) + \rho_3 Tbc(t) - X_2(t) [\sigma_1 + \beta(\text{HIV}^+) + \lambda'(\text{TB}) + \mu] \quad (2)$$

$$\frac{dI_1(t)}{dt} = (\text{TB}) [\lambda X_1(t) + \lambda' X_2(t)] - I_1(t) [\rho_1 + \delta_1 + \beta(\text{HIV}^+) + \mu] \quad (3)$$

$$\frac{dTbc(t)}{dt} = \sigma_1 X_2(t) + \delta_1 I_1(t) - Tbc(t) [\rho_3 + \beta(\text{HIV}^+) + \mu + \theta] \quad (4)$$

$$\frac{dZ(t)}{dt} = a(t)Z(0) + \frac{\beta}{3} X_1(t)(\text{HIV}^+) - Z(t)[\lambda(\text{TB}) + \mu] \quad (5)$$

$$\frac{dY_1(t)}{dt} = a(t)Y_1(0) + \frac{\beta}{3} X_1(t)(\text{HIV}^+) - Y_1(t) [\gamma_1 + \gamma_2 + \lambda(\text{TB}) + \mu] \quad (6)$$

$$\frac{dY_2(t)}{dt} = a(t)Y_2(0) + \frac{\beta}{3}X_1(t)(\text{HIV}^+) - Y_2(t) [\omega_1 + \omega_2 + \lambda(\text{TB}) + \mu] \quad (7)$$

$$\frac{dY_3(t)}{dt} = a(t)Y_3(0) + \beta X_2(t)(\text{HIV}^+) + \rho_2 I_2(t) + \rho_4 Y_4(t) - Y_3(t) [\lambda''(\text{TB}) + \omega_5 + \sigma_2 + \mu] \quad (8)$$

$$\frac{dY_4(t)}{dt} = \sigma_2 Y_3(t) + \delta_2 I_3(t) + \beta(\text{HIV}^+) [I_1(t) + Tbc(t)] - Y_4(t) [\rho_4 + \xi + \mu + \theta] \quad (9)$$

$$\frac{d\text{ARC}_1(t)}{dt} = \gamma_1 Y_1(t) - \text{ARC}_1(t) [\lambda(\text{TB}) + \mu] \quad (10)$$

$$\frac{d\text{ARC}_2(t)}{dt} = \gamma_2 Y_1(t) - \text{ARC}_2(t) [\lambda(\text{TB}) + \omega_3 + \omega_4 + \mu] \quad (11)$$

$$\frac{dI_3(t)}{dt} = \lambda(\text{TB}) [Z(t) + Y_1(t) + \text{ARC}_1(t) + \text{ARC}_2(t)] + \lambda''(\text{TB}) Y_3(t) - I_2(t) [\delta_2 + \rho_2 + \mu] \quad (12)$$

$$\frac{dA_1(t)}{dt} = \omega_1 Y_3(t) + \omega_3 \text{ARC}_3(t) - A_1(t) [\mu + \alpha] \quad (13)$$

$$\frac{dA_2(t)}{dt} = \omega_3 Y_3(t) + \omega_4 \text{ARC}_3(t) - A_2(t) [\lambda(\text{TB}) + \mu + \alpha] \quad (14)$$

$$\frac{dA_3(t)}{dt} = \omega_5 Y_3(t) + \rho_5 A tbc(t) - A_3(t) [\lambda'''(\text{TB}) + \mu + \alpha + \sigma_3] \quad (15)$$

$$\frac{dATbc(t)}{dt} = \xi Y_4(t) + \sigma_3 A_3(t) + \lambda(\text{TB}) A_2(t) + \lambda'''(\text{TB}) A_3(t) - ATbc(t) [\mu + \alpha + \theta + \rho_5]. \quad (16)$$

The closed version assumes a total population  $N(t)$  that is a constant and equal to one. For this we assume an immigration rate  $a(t)$  as an entry into the susceptible and HIV-positive compartments ( $X_1(t)$ ,  $X_2(t)$ ,  $Z(t)$ ,  $Y_1(t)$ ,  $Y_1(t)$ , and  $Y_3(t)$ ). This immigration rate equals the sum of all mortality rates and is weighted by an expected proportion of each of these classes in the population as a whole.

This set of equations can be rewritten to describe the dynamics of the model for an open version which could mimic populations with variable size. For this equations (1), (2), (5)–(8) are now written as:

$$\frac{dX_1(t)}{dt} = \Lambda(t) - X_1(t) [\beta(\text{HIV}^+) + \lambda(\text{TB}) + \mu] \quad (1a)$$

$$\frac{dX_2(t)}{dt} = \rho_1 I_1(t) + \rho_3 Tbc(t) - X_2(t) [\sigma_1 + \beta(\text{HIV}^+) + \lambda'(\text{TB}) + \mu] \quad (2a)$$

$$\frac{dZ(t)}{dt} = \frac{\beta}{3} X_1(t)(\text{HIV}^+) - Z(t) [\lambda(\text{TB}) + \mu] \quad (5a)$$

$$\frac{dY_1(t)}{dt} = \frac{\beta}{3} X_1(t)(\text{HIV}^+) - Y_1(t) [\gamma_1 + \gamma_2 + \lambda(\text{TB}) + \mu] \quad (6a)$$

$$\frac{dY_2(t)}{dt} = \frac{\beta}{3} X_1(t)(\text{HIV}^+) - Y_2(t) [\omega_1 + \omega_2 + \lambda(\text{TB}) + \mu] \quad (7a)$$

$$\frac{dY_3(t)}{dt} = \beta X_2(t)(\text{HIV}^+) + \rho_2 I_2(t) + \rho_4 Y_4(t) - Y_3(t) [\lambda''(\text{TB}) + \omega_5 + \sigma_2 + \mu] \quad (8a)$$

$$\frac{dN(t)}{dt} = \Lambda(t) - \mu N(t) - \alpha [A_1(t) + A_2(t) + A_3(t) + ATbc(t)] - \theta [Tbc(t) + Y_4(t) + ATbc(t)], \quad (17)$$

where

$$\Lambda(t) = \kappa \left\{ 1 - \frac{N(t)}{N_{\max}} \right\} [X_1(t) + X_2(t) + I_1(t) + Tbc(t)]$$

is a density-dependent maternity function with birth rate  $\kappa$ .

This function assumes that only individuals from classes  $X_1$ ,  $X_2$ ,  $I_1$ , and  $Tbc$  are able to reproduce.

## SENSITIVITY ANALYSIS

Of the forty parameters of the model (including some additional proportions rates not presented in Table 1), a great number can be estimated from epidemiological knowledge of both diseases. However, the infection rates for HIV and TB ( $\beta$  and  $\lambda$ , respectively) are extremely difficult, if not impossible, to estimate directly. The sensitivity and equilibrium analysis techniques could provide some insights to the estimation of these parameters, once all the others are known with at least some degree of confidence.

For the situation where there are  $k$  functions, given by the column vector  $x \equiv \{x_i\}$ ,  $i = 1, \dots, k$ ; and  $p$  essential parameters indicated by  $\theta \equiv \{\theta_j\}$ ,  $j = 1, \dots, p$ , we have that [17]

$$\delta x = H\delta\theta \quad (18)$$

where

$$H = (h_{ij}) = \left\{ \frac{\partial x_i}{\partial \theta_j} \right\}. \quad (19)$$

The matrix  $H$  is the *sensitivity matrix*, whose individual elements  $h_{ij}$  are the sensitivity functions  $\frac{\partial x_i}{\partial \theta_j}$ . Two additional matrices are required for the sensitive analysis, namely

$$E = \frac{\partial f}{\partial x} = \left\{ \frac{\partial f_i}{\partial x_j} \right\}, \quad T = \frac{\partial f}{\partial \theta} = \left\{ \frac{\partial f_i}{\partial \theta_j} \right\}. \quad (20)$$

Now suppose that the vector  $\theta$  is subject to a multi-dimensional prior distribution, for which the covariance matrix is  $V(\theta)$ . It follows that the corresponding covariance matrix  $V(x)$  for the multi-dimensional distribution of the vector  $x$  is given by

$$V(x) = HV(\theta)H' \quad (21)$$

where the prime indicates transposition.

Assuming that the elements of  $V(\theta)$  have been derived from subjective prior estimates [17], and that all the  $\theta_j$  are uncorrelated, the covariance matrix  $V(\theta)$  is of diagonal form, namely

$$V(\theta) = \begin{pmatrix} \sigma_1^2 & 0 & \dots & 0 \\ 0 & \sigma_2^2 & \dots & 0 \\ 0 & 0 & \dots & 0 \\ 0 & 0 & \dots & \sigma_p^2 \end{pmatrix} \quad (22)$$

where  $\sigma_j^2 = \text{var}(\theta_j)$ .

Substituting (22) into (21) then gives

$$\text{var}(x_j) = \sum_{j=1}^p h_{ij}^2 \sigma_j^2 \quad (23)$$

where the sensitivity matrix is given by

$$H = -E^{-1}T. \quad (24)$$

Therefore, the parameters to which any given  $x_i$  is most sensitive will maximize  $\text{var}(x_i)$ .

As mentioned above, we derived the elements of  $V(\theta)$  from subjective prior estimates based on the current epidemiologic knowledge of both infections. So we performed the sensitivity analysis assuming, to begin with, an equal variance for all the model's parameters and calculated the variances of the variables according to equation (23). We also assumed that for the closed version of the model, there is no immigration rate to any compartment except the susceptible  $X_1$ . Under these conditions, all the model's variables showed to be most sensitive to  $\beta$ , the transmission rate for HIV. We then reduced the variance of  $\beta$  to zero and recalculated the variables' variances in order to estimate which would be the next parameter to which the model is most sensitive. We repeated this procedure until the last parameter. Table 3 shows the results of this analysis for  $\lambda$ , the transmission rate of tuberculosis. It is interesting to note that the model is practically insensitive to variations in  $\lambda$ . Only in the 9<sup>th</sup> iteration, the first variable ( $X_1$ ) presented its maximum variance for this parameter.

Table 3. Results of the sensitivity analysis for the parameter  $\lambda$ , the force of infection tuberculosis. Shown is the iteration number and the variable whose variance is maximized by changes in  $\lambda$ .

Variable	Iteration
$X_1(t)$	9 <sup>th</sup>
$A_1(t)$	11 <sup>th</sup>
$A_2(t)$	11 <sup>th</sup>
$A_3(t)$	12 <sup>th</sup>
$Tbc(t)$	14 <sup>th</sup>
$ARC_2(t)$	14 <sup>th</sup>
$X_2(t)$	17 <sup>th</sup>
$Z(t)$	18 <sup>th</sup>
$Y_1(t)$	19 <sup>th</sup>
$Y_2(t)$	19 <sup>th</sup>
$I_2(t)$	20 <sup>th</sup>

### EQUILIBRIUM ANALYSIS

Next we performed the equilibrium analysis. As the analytical solution for the equilibrium densities is not straightforward, we simulated the model numerically with all the parameters' values fixed, except for  $\beta$  and  $\lambda$ . For this we applied the Newton-Raphson method [18], which is basically an iterative solution of the equation

$$f(X_i + \delta X) = f(X_0) + \left. \frac{\partial f}{\partial X} \right|_{X_0}, \quad \delta X = 0 \quad (25)$$

where the vector  $f(X_i)$  is the right side of equations (1)-(16). The increment  $\delta X$  is then

$$\delta X = - \left[ \left. \frac{\partial f}{\partial X} \right|_{X_0} \right]^{-1} f(X_0). \quad (26)$$

The first solution for  $X_i$  is given by  $\frac{\partial f}{\partial x} = 0$ . Successive iterations are then performed by calculating

$$X_{i+1} = X_i + \delta X \quad (27)$$

in equation (25) until the difference between  $\{X_{(i+1)} - X_i\}$  is lower than a given criterium. This method allows the estimation of all the equilibrium solutions for equations (1)-(16) for a given set of parameters.

If we take either  $\beta$ , or  $\lambda$ , or both parameters as equal to zero, we have the trivial solution, that is, the absence of either (or both) disease. By calculating the eigenvalues of the Jacobian matrix associated with the system of equations (1)-(16), we can determine the stability of these equilibrium solutions. In case either  $\beta$  or  $\lambda$  (or both) are zero, i.e., the absence of either (or both) diseases, we have that all the eigenvalues have their real parts negatives, characterizing a stable equilibrium [19]. We then raise slowly the values of either  $\beta$  or  $\lambda$  (or both) until the stability of the trivial solution is broken, that is, when at least one of the real part of the eigenvalues of the Jacobian matrix turns to positive. This value of the parameter represents a threshold point, above which the disease persists, below which the disease disappears. They represent the infection rates that guarantee the Basic Reproductive Rates [20] to be greater than one. The threshold values found for these conditions and set of parameters are  $\beta = 0.245$  and  $\lambda = 1.013$ . The numerical solution for the equilibrium proportion of individuals and their respective eigenvalues, calculated with the set of parameters shown in Table 2, in the absence of immigration except for  $X_1$ , can be seen in Table 4.

Table 4. Numerical solution for the equilibrium proportion of the individuals and their respective eigenvalues.

Variable	Equilibrium Value	Eigenvalue
$X_1$	0.220705	$-8.130815 + 0.00000 i$
$X_2$	0.636428	$-6.165702 + 0.00000 i$
$I_1$	0.000485	$-1.588609 + 0.00000 i$
$Tbc$	0.014546	$-0.896678 - 0.00394 i$
$Z$	0.029969	$-0.896678 - 0.00394 i$
$Y_1$	0.002708	$-0.533974 + 0.00000 i$
$Y_2$	0.005855	$-0.170276 + 0.00000 i$
$Y_3$	0.049317	$-0.015750 - 0.00551 i$
$Y_4$	0.002032	$-0.015750 + 0.00551 i$
$ARC_1$	0.008261	$-0.046226 - 0.00624 i$
$ARC_2$	0.001717	$-0.046226 + 0.00624 i$
$A_1$	0.001311	$-0.336779 - 0.02918 i$
$A_2$	0.002494	$-0.336779 + 0.02918 i$
$A_3$	0.013034	$-0.382691 - 0.00112 i$
$ATbc$	0.010715	$-0.382691 + 0.00112 i$
$I_2$	0.000140	$-0.032788 + 0.00000 i$

## SIMULATIONS OF THE MODEL

In order to study the model's dynamics, we performed numerical simulations for both the open and closed versions. As mentioned above, since the qualitative outcomes of either versions are very similar, we shall present in this paper only the results of the closed one. Information on the main epidemiological parameters determining transmission is slowly accumulating, but much uncertainty remains. The major features of HIV infection and disease culled from some of the more extensive studies have been recently reviewed by Anderson *et al.* [21]. For the estimation of the set of parameters required for the simulation here performed, we applied the "Method of Varying Parameters to Match the Data," described by Kault and Marsh [22], along with the equilibrium analysis described above, which resulted in plausible values for current epidemiological knowledge.

In this set of simulations, we study the relative distribution of individuals among susceptible, asymptomatic carriers and those with active disease for both infections. We are particularly interested in demonstrating the mutual influence of both infections.

Figure 2 shows the time variation of the ratio between the proportion of AIDS cases and HIV-positive individuals. The lower curve represents this ratio in the absence of tuberculosis, whilst the upper one represents the same ratio in the presence of both infections. It can be noted that in the presence of tuberculosis there is a marked increase in the relative proportion of AIDS cases as related to total HIV infection.

Figure 3 shows a similar analysis for the ratio between the proportions of active and latent cases of tuberculosis in the absence and presence of HIV infection for the lower and upper curves, respectively. Again there is a substantial increase in the relative amount of active tuberculosis in the presence of AIDS.

In Figure 4, it is shown how the prevalence of AIDS varies as a function of tuberculosis incidence. The lower curve represents the time variation of AIDS prevalence in the absence of tuberculosis. The set of upper curves shows the increase in AIDS prevalence with growing tuberculosis incidence.

The equivalent situation is shown in Figure 5, which displays the time variation in the prevalence of tuberculosis as a function of HIV incidence. It can be noted that, similarly to Figure 4, there is an increase in tuberculosis prevalence with growing values of HIV incidence.



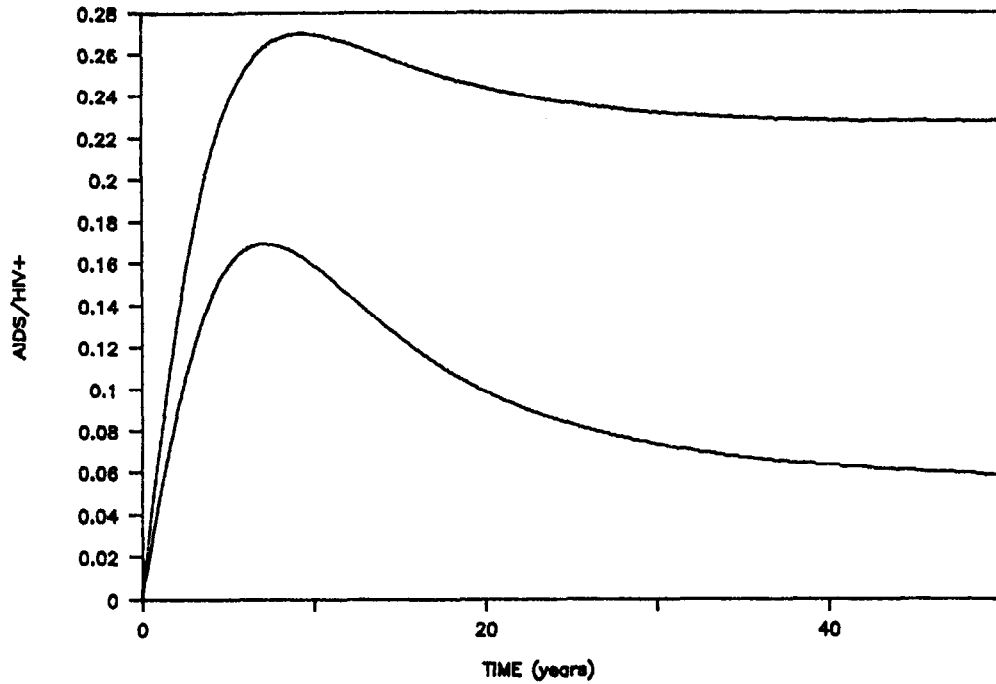


Figure 2. Time variation of the ratio AIDS/HIV<sup>+</sup> in the absence (lower curve) and presence of tuberculosis (upper curve).

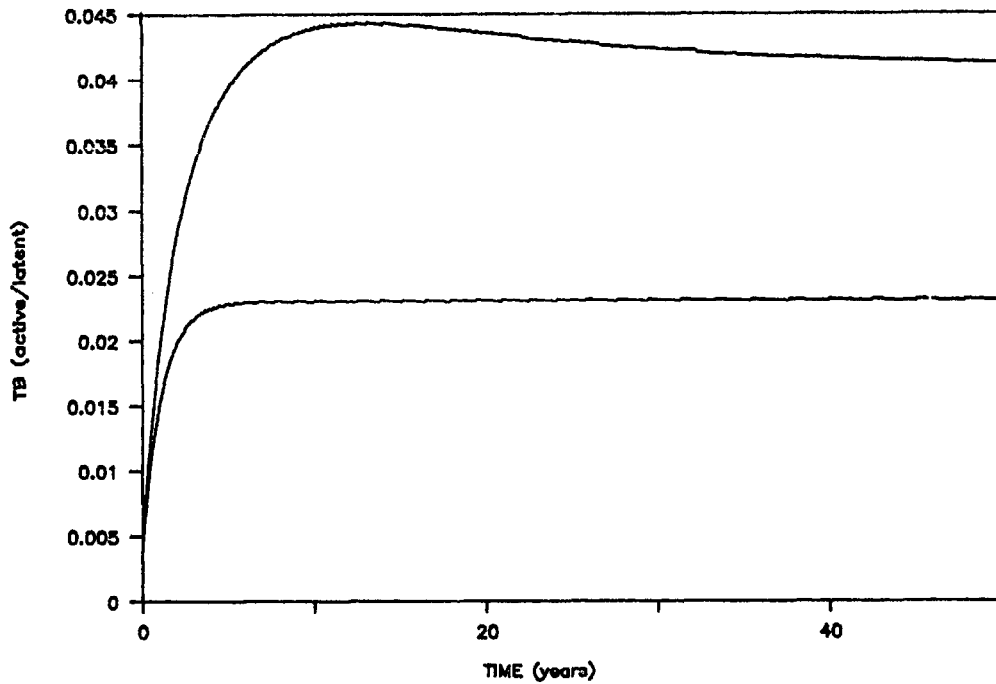


Figure 3. Time variation of the ratio active/latent TB in the absence (lower curve) and presence of AIDS (upper curve).

### ANALYSIS OF THE INTERACTION BETWEEN HIV AND TB

In this section, we present the results of the epidemiological analysis aiming to quantify the interaction between HIV and TB infection as predicted by the model. For this we estimated the Relative Risk (RR) [23] of developing AIDS given that one is exposed to TB, and the other way around, the RR of developing active TB once exposed to HIV. As we simulated the model for a period of 50 years, our results should be expressed by the Incidence Density Ratio, which is the most commonly applied indicator of RR in 'follow-up' studies [24].

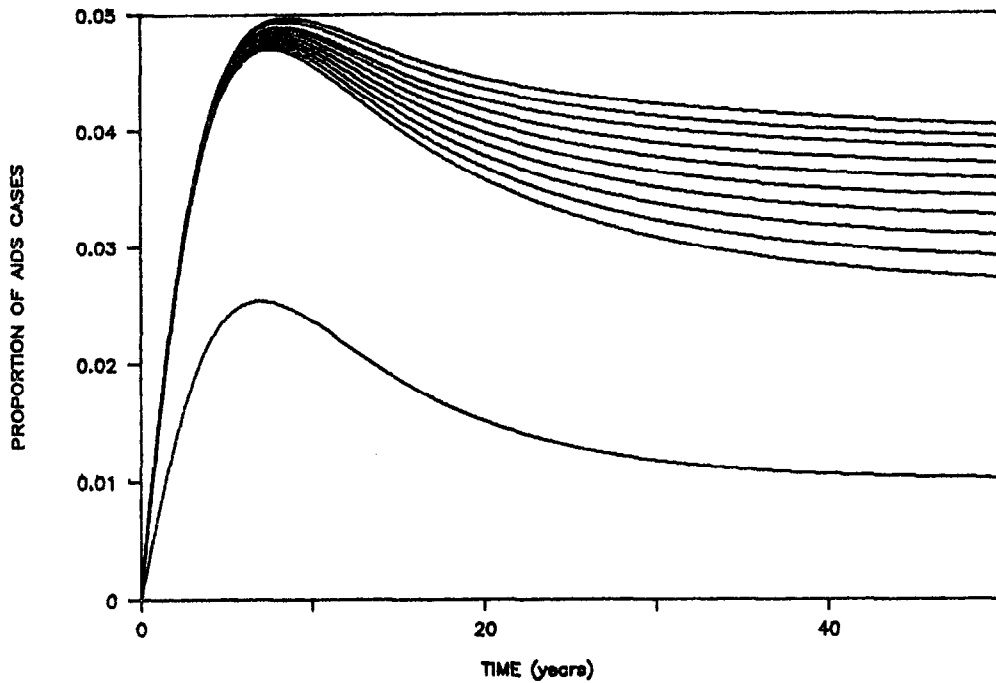


Figure 4. Time variation of AIDS prevalence in the absence of tuberculosis (lower curve) and crescent incidence of tuberculosis (upper set of curves).

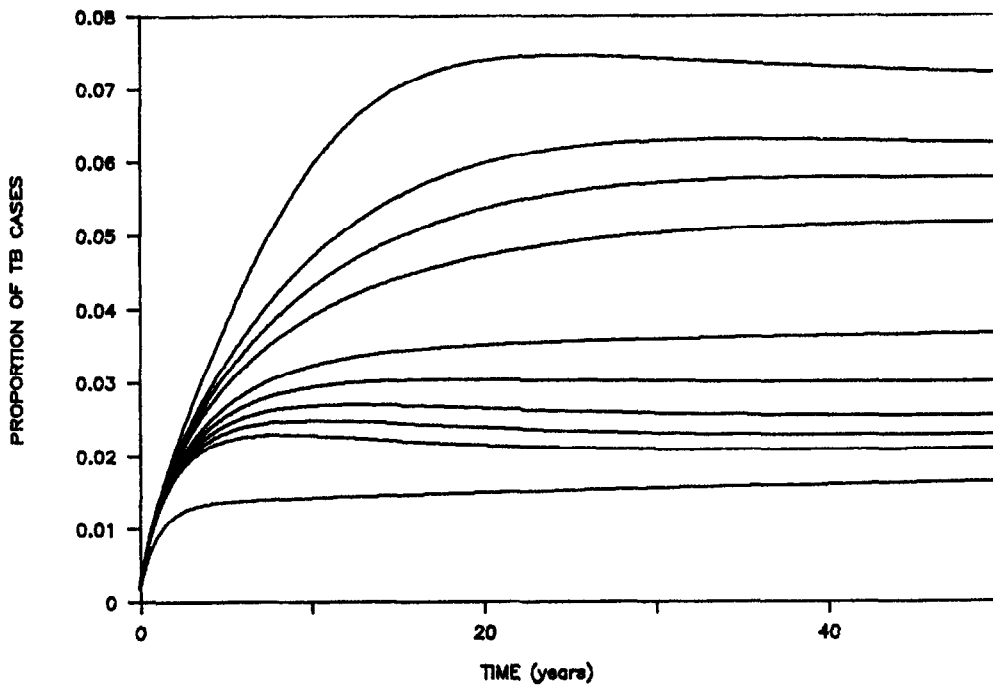


Figure 5. Time variation of TB prevalence in the absence of AIDS (lower curve) and crescent incidence of AIDS (upper set of curves).

The Incidence Density Ratio is defined as the ratio of the number of affected individuals among all the exposed to a potential risk factor, to the number of affected individuals among all the non-exposed to the same factor [23]. So, in the classical  $2 \times 2$  table of the form:

	exposed	non-exposed
affected	A	B
non-affected	C	D

the Incidence Density Ratio would be:

$$\text{IDR} = \frac{\frac{A}{(A+C)}}{\frac{B}{(B+D)}}.$$

For the estimation of the relative risk of developing AIDS once exposed to TB, we consider the total number of AIDS cases and susceptible after fifty years of simulation with the transmission rate of TB,  $\lambda$ , varying from 0.5 to 2 and 0, for the exposed and non-exposed conditions, respectively. Figure 6 shows the result of this analysis. It can be noted that the risk of developing AIDS in the presence of TB rapidly raises to around 2.5 times greater than in its absence, and varies very little with further increases in the values of TB incidence.

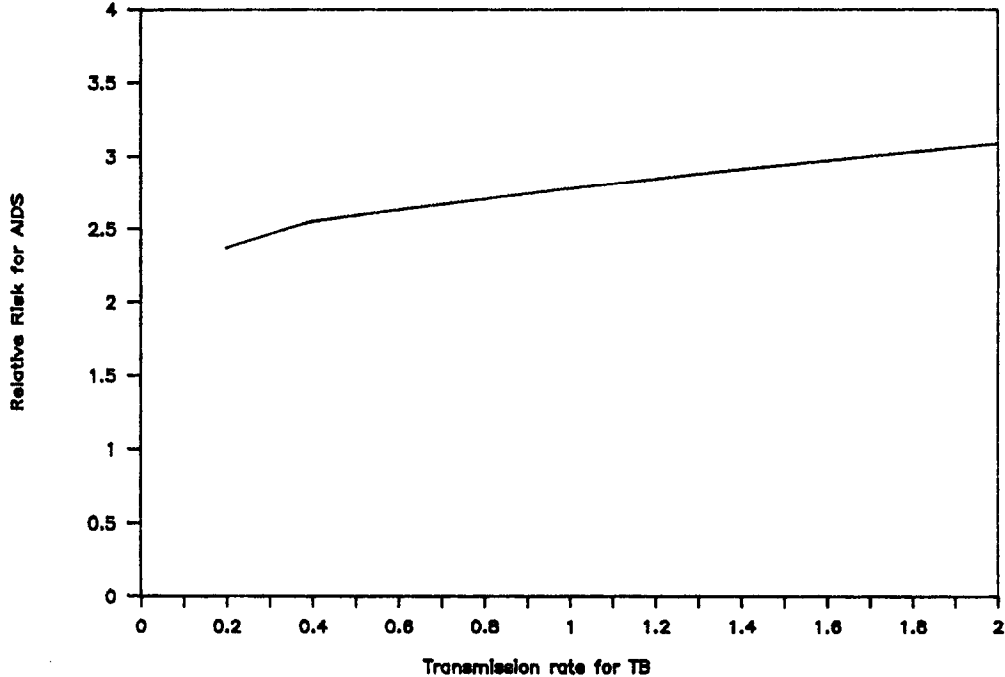


Figure 6. Relative risk of developing AIDS as a function of TB incidence.

By the same token, we consider, for the estimation of the relative risk of developing tuberculosis once exposed to HIV, the total number of TB cases and susceptible after fifty years of simulation with the transmission rate of HIV,  $\beta$ , varying from 0.05 to 0.6 and 0, for the exposed and non-exposed conditions, respectively. The result of this analysis is shown in Figure 7. It can be noted that the relative risk of developing tuberculosis once exposed to HIV raises exponentially with the increasing in the HIV incidence, from about 1.5 to almost 11 times greater than in its absence. This remarkable difference in the model behaviour should be expected from the sensitivity analysis results, which demonstrated a greater sensitivity of the model to the HIV incidence rate  $\beta$ , and is in accord with the current epidemiological observations.

An interesting alternative way to qualitatively understand the interaction between both infections is to analyze how the effective reproductive rate,  $R$ , varies as a function of the proportion of remaining susceptible  $X(t)$ . The effective reproductive rate is usually defined as the average number of secondary infections caused by each infectious individual [20]. It contrasts with the basic reproductive rate,  $R_0$ , which is defined as the average number of secondary infections produced by a single infectious individual in an entirely susceptible population. The effective and the basic reproductive rates are related, under the “weak homogeneously mixing” assumption by [20]:

$$R = R_0 X(t), \quad (28)$$

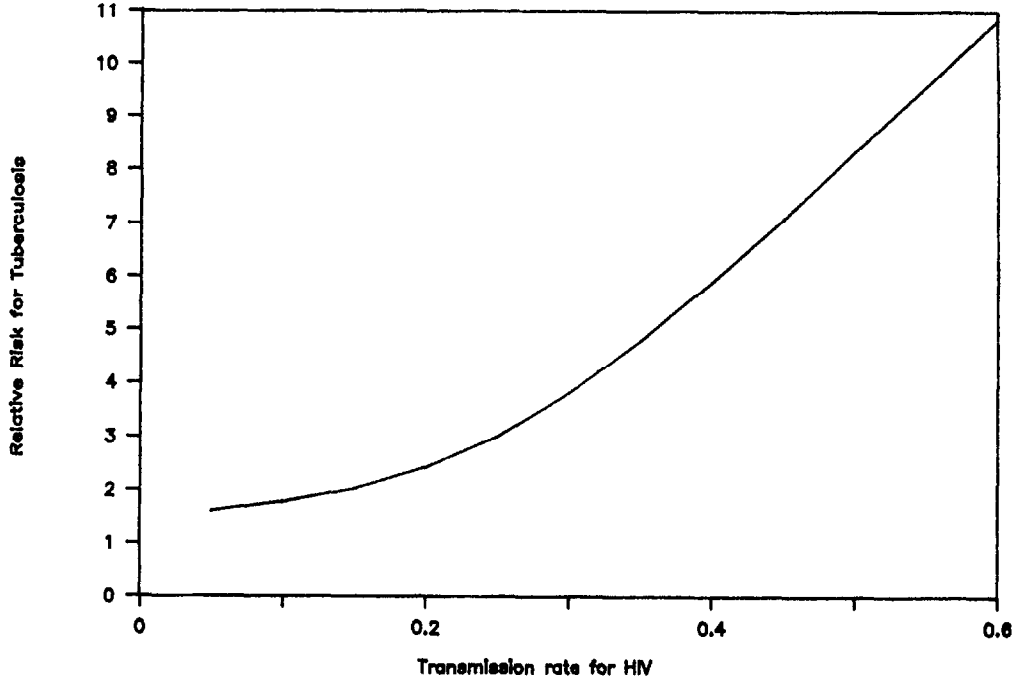


Figure 7. Relative risk of developing active TB as a function of AIDS incidence.

where  $X(t)$  in our model is the sum of  $X_1(t) + X_2(t)$ . Solving equations (1) and (2) for  $X_1(t)$  and  $X_2(t)$  we have:

$$X_1(t) = \left[ X_1(0) + \int_0^t a(S) e^{\int_0^S F_1(s') ds'} dS \right] e^{-\int_0^t F_1(s') ds'}, \quad (29)$$

where

$$F_1(t) = [\beta(\text{HIV}^+ + \mu) + \lambda(\text{TB})]$$

with  $a(t)$ ,  $\text{HIV}^+$ , and  $(\text{TB})$  as defined before and

$$X_2(t) = \left[ X_2(0) + \int_0^t F_2(S) e^{\int_0^S F_1(s') ds'} \right] e^{\int_0^t F_1(s') ds'}, \quad (30)$$

where

$$F_2(t) = \rho_1 I_1(t) + \rho_2 Tbc(t)$$

and

$$F_3(t) = \sigma_1 + [\beta(\text{HIV}^+ + \mu) + \lambda'(\text{TB})].$$

Now, knowing the basic reproductive rate for AIDS and tuberculosis, one can assess the time variation of the effective reproductive rate for either infection. It can be noted from equations (29) and (30) that the effective reproductive rate for AIDS is dependent on both AIDS and tuberculosis prevalence, and the other way around, the effective reproductive rate is also depending on the presence of both infections. This is due to the fact that the proportion of remaining susceptible varies as a function of both infections.

## DISCUSSION

The model presented here combines the structures of models previously reported for AIDS [25] and for tuberculosis [26] including the complexities resulting from the interaction of two infections. It should be clear that our aim is to provide a theoretical framework allowing the analysis of the dynamic interaction of two distinct infections on the same host population. This paper intends to present the model's structure and the analysis of its theoretical consistency, and to check

whether it fulfils the Pilz and Tautu [27] definition, according to which “the aim of mathematical modelling is the examination of natural processes and phenomena in an abstract and logically coherent manner.”

There are several other models for the HIV transmission that could have been chosen to study its interaction with tuberculosis. The specialized literature abounds with such models (see a recent review by Anderson *et al.* [21] and every new issue of those periodicals presents a new one. On the other hand, there are few models for tuberculosis. Since the seminal papers by Waaler *et al.* [28–30], ReVelle [26], and Azuma [31] in the late sixties and early seventies, few authors have addressed this subject. This is probably due to the fact that tuberculosis ceased to be a public health problem in the developed countries, despite the fact that this disease has never lost its grip of human lives in developing countries. This picture, however, was dramatically reversed with the advent of AIDS pandemic.

Due to its particularities, AIDS is a syndrome characterized by the interaction of HIV with other infections. This is particularly true for tuberculosis. It is therefore surprising how few works have investigated the dynamics of these interactions. Some exceptions are the papers by Kault and March [22], and that by Pepin *et al.* [32], who proposed a model of AIDS as a function of other sexually transmitted diseases, and that a schematic representation for the interactions between HIV infection and tropical diseases which has a structure quite similar to our model, although these authors do not propose any dynamic model associated with their scheme.

Biological realities not considered at this stage, like the heterogeneity in sexual contacts, described by Anderson [33], and the likely distributions of HIV incubation periods, described by Bhythe and Anderson [34], could be easily incorporated into the model. Also, intervention strategies, like treatment of active tuberculosis and/or HIV-positive individuals, chemoprophylaxis or vaccination against tuberculosis can be included simply by modifying some transition rates or by appending new compartments on the model.

Co-infection is represented by a parallel structure which allows the analysis of either disease individually or the concomitant occurrence of both infections, highlighting, therefore their mutual influence and the qualitatively distinct outcomes that results. This structure demands the inclusion of new compartments, which represents the co-infection states, namely  $Y_3$ ,  $Y_4$ ,  $I_2$ ,  $A_3$ , and  $ATbc$ . Note that the first three compartments reproduce the structure proposed for describing the dynamics of tuberculosis, in the presence of HIV infection. However, when we consider the full-blown AIDS compartments, this structure is simplified, since it is not reasonable to accept the evolution of primary TB infection to a latent form of disease in this situation.

Other compartments representing theoretical possibilities were considered. The fraction of individuals infected by HIV and who do not evolve to full-blown AIDS, unless infected by TB, represented in the model by the compartment  $Z(t)$ , although not universally accepted, is a possibility that should be considered in a theoretical study like this. The so-called AIDS-Related-Complex condition is also questionable from the epidemiological point of view since it evolves to full-blown AIDS by the same manner as  $HIV^+$  do. It must be noted that the clinical definition of AIDS was changed in 1987 [35] and that the use of the ARC diagnosis has been discontinued by some medical practitioners. However, ARC diagnosis has not been abandoned and, when present, provides additional information. Also, in this case, we consider the possibility of some of such individuals remaining as ARC in the absence of a co-infection. Finally, the compartment representing  $HIV^+$  individuals with active TB, ( $Y_4$ ) may be questioned depending on the AIDS definition adopted and on the epidemiological background of the involved population. So, in populations with high levels of TB prevalence, it seems reasonable to consider the existence of such state.

The sensitivity analysis pointed to  $\beta$  as the parameter to which the model is, by far, most sensitive. On the other hand, the model showed a very low degree of sensitivity to  $\lambda$ , the parameter that, along with  $\beta$ , is associated with the non-linear terms of the model. This is probably due to the fact that, contrasting with HIV, there is spontaneous recovery for TB infection. This high sensitivity to  $\beta$  is in agreement with current epidemiological expectancies and may help the design of control strategies.

The difference found between the threshold values for  $\beta$  and  $\lambda$  may be surprising at first sight since the basic reproductive rate is probably greater for TB than for AIDS. It should be remarked

that the threshold values found are ones which cause  $R_0$  to be greater than one. As the period of time individuals spend in the infectious states is much greater for AIDS than TB, the difference found is to be expected. The threshold values were calculated from the equilibrium situation in which both infections were absent. The same method can be applied for threshold estimations with either infection present at equilibrium. The results of such calculations will be reported in a future paper.

The numerical simulations were performed to illustrate the model's dynamics and resulted in three striking outcomes, regarding the mutual influences of both infections. First, the pathogenicity of HIV is enhanced by the presence of TB, and vice-versa, as shown in Figures 2 and 3. Second, the prevalence of AIDS almost doubled in the presence of TB as shown by the lowest line of the upper set of curves of Figure 4. It can be noted that further increases in TB incidence correspond to increases in AIDS prevalence levels. Figure 5 shows that the increase in HIV incidence levels result also in an increase in TB prevalence, although with a distinct pattern. Third, Figures 6 and 7 show the results of the relative risk analysis and demonstrate clearly that there is a much stronger influence of AIDS on TB than the other way around. This aspect may account for the differences mentioned above.

We think the model fulfils its objectives and has proven to be logically coherent, providing outcomes that are in accord with current epidemiological expectancies. It could, therefore, be used as a template upon which alternative control strategies could be tested, like treatment and vaccination schedules. It also provides insights into the epidemiological interaction between AIDS and TB, that poses questions that should be tested in the field. This induced us to design a cohort study in a South American prison in order to check the model's outcomes, which will be carried out in the near future.

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