OPERATIONS RESEARCH
Vol. 56, No. 6, November–December 2008, pp. 1366–1381
ISSN 0030-364X | EISSN 1526-5463 | 08 | 5606 | 1366

informs

DOI 10.1287/opre.1080.0571

Controlling Co-Epidemics: Analysis of HIV and Tuberculosis Infection Dynamics

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A co-epidemic arises when the spread of one infectious disease stimulates the spread of another infectious disease. Recently, this has happened with human immunodeficiency virus (HIV) and tuberculosis (TB). We develop two variants of a co-epidemic model of two diseases. We calculate the basic reproduction number (R_0), the disease-free equilibrium, and the quasi-disease-free equilibria, which we define as the existence of one disease along with the complete eradication of the other disease, and the co-infection equilibria for specific conditions. We determine stability criteria for the disease-free and quasi-disease-free equilibria. We present an illustrative numerical analysis of the HIV-TB co-epidemics in India that we use to explore the effects of hypothetical prevention and treatment scenarios. Our numerical analysis demonstrates that exclusively treating HIV or TB may reduce the targeted epidemic, but can subsequently exacerbate the other epidemic. Our analyses suggest that coordinated treatment efforts that include highly active antiretroviral therapy for HIV, latent TB prophylaxis, and active TB treatment may be necessary to slow the HIV-TB co-epidemic. However, treatment alone may not be sufficient to eradicate both diseases. Increased disease prevention efforts (for example, those that promote condom use) may also be needed to extinguish this co-epidemic. Our simple model of two synergistic infectious disease epidemics illustrates the importance of including the effects of each disease on the transmission and progression of the other disease.

Subject classifications: health care: epidemiology, treatment; simulation: applications; infectious disease co-epidemic; epidemic control; HIV; tuberculosis; India.
Area of review: Special Issue on Operations Research in Health Care.
History: Received December 2006; revisions received May 2007, October 2007, November 2007, December 2007; accepted December 2007.

1. Introduction

Co-epidemics—the related spread of two or more infectious diseases—have afflicted mankind for centuries. Worldwide, almost 40 million people were living with HIV/AIDS in 2005, with the majority of infections occurring in developing countries (Joint United Nations Programme on HIV/AIDS 2006). Approximately one-third of people in the world today are infected with tuberculosis (latent TB), and nine million people develop tuberculosis disease (active TB) every year, with 90% of all active TB cases occurring in developing countries (Joint United Nations Programme on HIV/AIDS 2006, Global Fund 2006). In the world's hardest hit regions, including sub-Saharan Africa and Southeast Asia, there is strong evidence that HIV and TB are inextricably linked (WHO 2006e).

HIV and TB exhibit a unique symbiosis, despite biological differences. HIV is a retrovirus that is transmitted primarily by homosexual and heterosexual contact, needle-sharing, and from mother to child. The disease eventually progresses to AIDS as the immune system weakens. HIV can be treated with highly active antiretroviral therapy (HAART), but there is presently no cure (NIAID 2005). Virtually all HIV-infected individuals can transmit the virus to others, and an infected individual's chance of spreading the virus generally increases as the disease progresses and damages the immune system (Sanders et al. 2005). Tuberculosis is caused by *mycobacterium tuberculosis* bacteria and is spread through the air. Infected individuals may have latent TB and not feel ill, or they may develop active TB, which can cause severe symptoms. Individuals with active TB can then infect others, leading to latent TB in the newly infected individual. Those with latent TB can be given preventive therapy to avoid developing active TB, and active TB can be treated with antibiotics.

HIV and TB have a synergistic relationship; the presence of one disease exacerbates the other. Individuals infected with HIV are particularly susceptible to acquiring TB infection (WHO 2006c). TB increases an individual's rate of progression from asymptomatic HIV to AIDS, and shortens survival time (AVERT.ORG 2006a, WHO 2006c). An HIV-infected individual with latent TB is 50 times more likely to develop active TB in a given year than an individual

not infected with HIV (AVERT.ORG 2006a, WHO 2006c). TB accounts for almost one-third of all AIDS deaths worldwide, and if left untreated, active TB almost always leads to death in HIV-infected individuals (AVERT.ORG 2006a; WHO 2006c, d).

The study of infectious disease co-epidemics is critical to understanding how the diseases are related, and how prevention and treatment efforts can be most effective. Mathematical models can provide insight into the complicated infection dynamics, and into effective control measures. Most mathematical epidemic models evaluate a single disease (Anderson and May 1991, Kermack and McKendrick 1927), although a growing number of studies have considered co-epidemics.

Some authors have developed simulation models to investigate HIV-TB co-epidemic dynamics. West and Thompson (1997) simulated the effect of HIV on the TB epidemic, without considering prevention and treatment. Porco et al. (2001) created a discrete-event simulation model of HIV and TB co-infection, and considered different mixing patterns. Currie et al. (2003) combined a dynamic HIV model with a statistical TB model to compare latent TB prophylaxis, active TB treatment, case detection, and HIV prevention and treatment. Williams et al. (2005) extended an earlier model (Dye et al. 1998) to examine the effects of HIV and TB treatment. Dowdy et al. (2006) created a model of HIV and TB with a constant risk of acquiring either disease, and simulated the effects of improved TB diagnostic techniques, case finding, and HIV treatment. Cohen et al. (2006) used a deterministic transmission model that included parallel HIV and TB submodels to evaluate the effect of latent TB prophylaxis in individuals coinfected with HIV.

Limited research has been conducted on the analytical understanding of co-epidemics, such as the effect of treatment regimens on the basic reproduction number and the stability of epidemic equilibria. Castillo-Chavez and Song (2004) summarized recent research on modeling TB, including the effect of HIV transmission. Naresh and Tripathi (2005) developed a simple HIV-TB co-epidemic model and performed stability and numerical analysis. However, the model excluded co-infection, greatly simplified infection dynamics, included few disease states (e.g., the important distinction between latent and active TB was absent), and assumed HIV treatment was unavailable. Blyuss and Kyrychko (2005) developed a symmetric co-epidemic model with two disease states, analyzed equilibria stability, and showed how variations in parameter values affected equilibria. This model is similar to one variant of a model that we present (the SI × SI model). However, we perform additional global stability analysis, analyze the co-infection equilibrium, and extend the model to include disease recovery. We also present an asymmetric co-infection model (the SII × SEI model).

In this paper, we develop two models of co-epidemics with two diseases. We first develop an SI × SI model in which each disease has two infection states, susceptible and infected (§2). We then develop an SII × SEI model in which one disease has three states (susceptible, infected with no symptoms, and infected with symptoms), and the other disease has three different states (susceptible, exposed, and infected) (§3). For each model, we analyze the disease-free equilibrium (DFE); we develop new terminology for quasi-disease-free equlibria (QDFE); and we characterize these points and the basic reproduction number, R_0. We derive the co-infection equilibrium (CIE) for a particular case of the SI × SI model, and we show numerically the conditions for the existence of the CIE. We use the DFE, QDFE, and CIE to characterize the conditions under which one or both diseases can be eradicated. We apply the SII × SEI model using data for the HIV-TB co-epidemics in India and we perform illustrative numerical analysis (§4). We evaluate hypothetical prevention and treatment scenarios to gain insight into the infection dynamics, and we compare the numerical results obtained from a co-epidemic model with results from two single-disease models. We summarize our findings and conclude with discussion (§5).

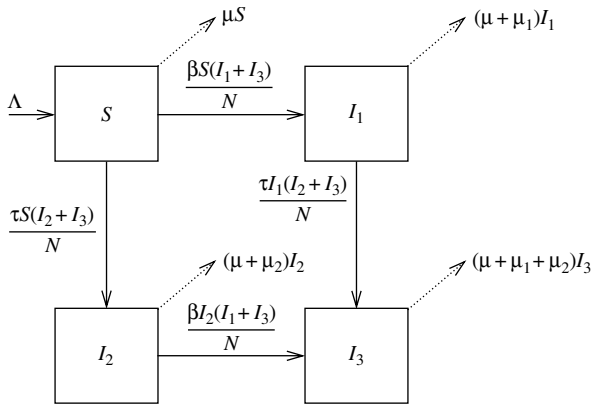
2. SI × SI Model

2.1. SI × SI Model Formulation

We first develop a simple compartmental model for a co-epidemic of two diseases, each of which has two states, susceptible and infected (Figure 1). The population of interest is subdivided into four mutually exclusive and collectively exhaustive compartments: susceptible to both diseases (S), infected with disease 1 and susceptible to disease 2 (I_1), infected with disease 2 and susceptible to disease 1 (I_2), and infected with both diseases (I_3). We refer to this as an SI × SI model.

We model the co-epidemic using a system of nonlinear differential equations. We denote the number of people

Figure 1. Schematic diagram of the SI × SI model.



Notes. The boxes represent cohorts of individuals and the arrows represent disease transmission, maturation, or death. S = susceptible to both diseases, I_1 = infected with disease 1, I_2 = infected with disease 2, I_3 = infected with both diseases.

in each compartment at time t by $S(t)$, $I_1(t)$, $I_2(t)$, and $I_3(t)$, and the total population size at time t by $N(t) \equiv S(t) + I_1(t) + I_2(t) + I_3(t)$. We assume that disease transmission occurs via random mixing between members in the susceptible and infected compartments. We denote the sufficient contact rates for diseases 1 and 2 by β and τ, respectively. Individuals can only contract one disease at a time (individuals cannot transition directly from S to I_3). We denote the natural death rate in the population by μ, the death rate from disease 1 by μ_1, and the death rate from disease 2 by μ_2. We allow the sufficient contact and mortality rates to vary between disease 1 and disease 2 to capture the key differences in disease characteristics. For simplicity, we assume that these parameters do not change for coinfected individuals. We assume a constant rate of new entries into the population, which we denote by Λ. All parameters are assumed to be nonnegative. Mathematically, we write this model as

$$\frac{dS}{dt} = \Lambda - \beta(I_1 + I_3)\frac{S}{N} - \tau(I_2 + I_3)\frac{S}{N} - \mu S, \tag{1}$$

$$\frac{dI_1}{dt} = \beta(I_1 + I_3)\frac{S}{N} - \tau(I_2 + I_3)\frac{I_1}{N} - (\mu + \mu_1)I_1, \tag{2}$$

$$\frac{dI_2}{dt} = \tau(I_2 + I_3)\frac{S}{N} - \beta(I_1 + I_3)\frac{I_2}{N} - (\mu + \mu_2)I_2, \tag{3}$$

$$\frac{dI_3}{dt} = \beta(I_1 + I_3)\frac{I_2}{N} + \tau(I_2 + I_3)\frac{I_1}{N} - (\mu + \mu_1 + \mu_2)I_3. \tag{4}$$

In vector form, we represent the compartment sizes as (S, I_1, I_2, I_3).

In the following section, we calculate the basic reproduction number, which characterizes the long-term sustainability of an infectious disease in a population. We then analytically derive the disease-free equilibrium, a condition where both diseases are eradicated, and determine local and global stability criteria. We determine the local stability conditions for the quasi-disease-free equilibria, which occur when only one disease is completely eradicated. We characterize the co-infection equilibrium, a state in which both diseases persist, under a particular simplifying assumption. We conclude discussion of the SI × SI model with illustrative numerical analysis of the equilibria. In Online Appendix B, we extend the SI × SI model to include recovery from disease. An electronic companion to this paper is available as part of the online version that can be found at http://or.journal.informs.org/.

2.2. Basic Reproduction Number

The basic reproduction number, R_0, is defined as the effective number of secondary infections caused by a typical infected individual during his entire period of infectiousness (Diekmann et al. 1990). We calculate R_0 by using the next generation operator method (van den Driessche and Watmough 2002). Additional details are provided in Online Appendix A.

$$R_0 = \max\{R_0^1, R_0^2\}, \tag{5}$$

where

$$R_0^1 = \frac{\beta}{\mu + \mu_1}, \qquad R_0^2 = \frac{\tau}{\mu + \mu_2}.$$

We can interpret the formula for R_0 by examining two separate single-disease models, where only disease j $(j = 1, 2)$ is present in the population:

$$\frac{dS}{dt} = \Lambda - \beta_j I_j \frac{S}{N} - \mu S,$$

$$\frac{dI_j}{dt} = \beta_j I_j \frac{S}{N} - (\mu + \mu_j)I_j,$$

$$N = S + I_j.$$

The terms R_0^1 and R_0^2 (from the co-epidemic model) coincide with the single-disease basic reproduction numbers for diseases 1 and 2, respectively. The overall co-epidemic basic reproduction number, R_0, equals the maximum of R_0^1 and R_0^2 because the corresponding disease will dominate.

2.3. SI × SI Model Equilibria Analysis

2.3.1. Disease-Free Equilibrium (DFE). The disease-free equilibrium (DFE) is an equilibrium where no individuals in the population are infected with any disease; this condition implies $I_1 = I_2 = I_3 = 0$. Substituting these values into the system (1)–(4) and solving

$$\frac{dS}{dt} = \frac{dI_1}{dt} = \frac{dI_2}{dt} = \frac{dI_3}{dt} = 0$$

leads to the following disease-free equilibrium, E_0:

$$E_0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0\right). \tag{6}$$

We can show that E_0 is locally stable or globally asymptotically stable provided certain conditions are fulfilled.

Proposition 1 (Local Stability of DFE in the SI × SI Model). *The disease-free equilibrium E_0 is locally asymptotically stable if* $R_0 < 1$.

Proposition 2 (Global Stability of DFE in the SI × SI Model). *Suppose that*

$$\max\left\{\frac{\beta}{\mu + \mu_1}, \frac{\tau}{\mu + \mu_2}, \frac{\beta + \tau}{\mu + \mu_1 + \mu_2}\right\} < \frac{1}{2}. \tag{7}$$

Then, the disease-free equilibrium E_0 is globally asymptotically stable.

The proof of Proposition 2 and all subsequent proofs are in Online Appendix A. In Equation (7), the terms in the maximization set correspond to compartments I_1, I_2, and I_3, respectively. Within each term, the numerator represents the force of infection (i.e., the transmission rate by infected individuals in the corresponding compartment), and the denominator is the removal rate of infected individuals. If the replacement rate of infected individuals is not sufficiently high, both diseases are eradicated and the DFE is globally stable.

2.3.2. Quasi-Disease-Free Equilibria (QDFE). We define the quasi-disease-free equilibrium (QDFE) as an equilibrium where infected individuals all have either disease 1 or disease 2, and the other disease is not present

in the population. This condition implies either $I_1 > 0$, $I_2 = I_3 = 0$ or $I_2 > 0$, $I_1 = I_3 = 0$. We calculate two quasi-disease-free equilibria and local stability conditions. Additional details are provided in Online Appendix A.

First QDFE. For the first QDFE, E_1, only the first disease is present, so $I_2 = I_3 = 0$. We calculate the first QDFE to be

$$E_1 = \left(\frac{\Lambda}{\beta - \mu_1}, \frac{\Lambda(\mathrm{R}_0^1 - 1)}{\beta - \mu_1}, 0, 0\right). \quad (8)$$

E_1 exists if $\mathrm{R}_0^1 > 1$.

Proposition 3 (Local Stability of First QDFE in the SI × SI Model). *The first QDFE, E_1, is locally asymptotically stable provided that*

$$\mu + \mu_1 + \mu_2 > \tau\left[1 + \frac{\mu_1}{\mathrm{R}_0^1(\beta - \mu_1 + \mu_2)}\right]. \quad (9)$$

Second QDFE. The second QDFE, E_2, exists when only the second disease is present: $I_1 = I_3 = 0$.

$$E_2 = \left(\frac{\Lambda}{\tau - \mu_2}, 0, \frac{\Lambda(\mathrm{R}_0^2 - 1)}{\tau - \mu_2}, 0\right). \quad (10)$$

E_2 exists if $\mathrm{R}_0^2 > 1$.

Proposition 4 (Local Stability of Second QDFE in the SI × SI Model). *The second QDFE, E_2, is locally asymptotically stable provided that*

$$\mu + \mu_1 + \mu_2 > \beta\left[1 + \frac{\mu_2}{\mathrm{R}_0^2(\tau + \mu_1 - \mu_2)}\right]. \quad (11)$$

We have characterized scenarios where neither disease persists (Proposition 1), only disease 1 persists (Proposition 3), or only disease 2 persists (Proposition 4). We now discuss the case when both diseases persist (i.e., the co-infection equilibrium).

2.3.3. Co-Infection Equilibrium (CIE). We define the co-infection equilibrium (CIE) as an equilibrium in which some co-infection exists. For the SI × SI model, this implies $I_3 > 0$. To solve for the CIE, we set Equations (1)–(4) equal to zero. We are unable to obtain a closed-form solution for the CIE, in general. However, in the case where disease mortality is minimal, we can approximate this by assuming $\mu_1 = \mu_2 = 0$. Then, we obtain the following analytical solution for the CIE, E_3:

$$E_3 = \left(\frac{\Lambda}{(\beta + \tau - \mu)}, \frac{\Lambda(\beta - \mu)}{\tau(\beta + \tau - \mu)}, \frac{\Lambda(\tau - \mu)}{\beta(\beta + \tau - \mu)}, \frac{\Lambda(\beta + \tau)(\beta - \mu)(\tau - \mu)}{\beta\tau\mu(\beta + \tau - \mu)}\right). \quad (12)$$

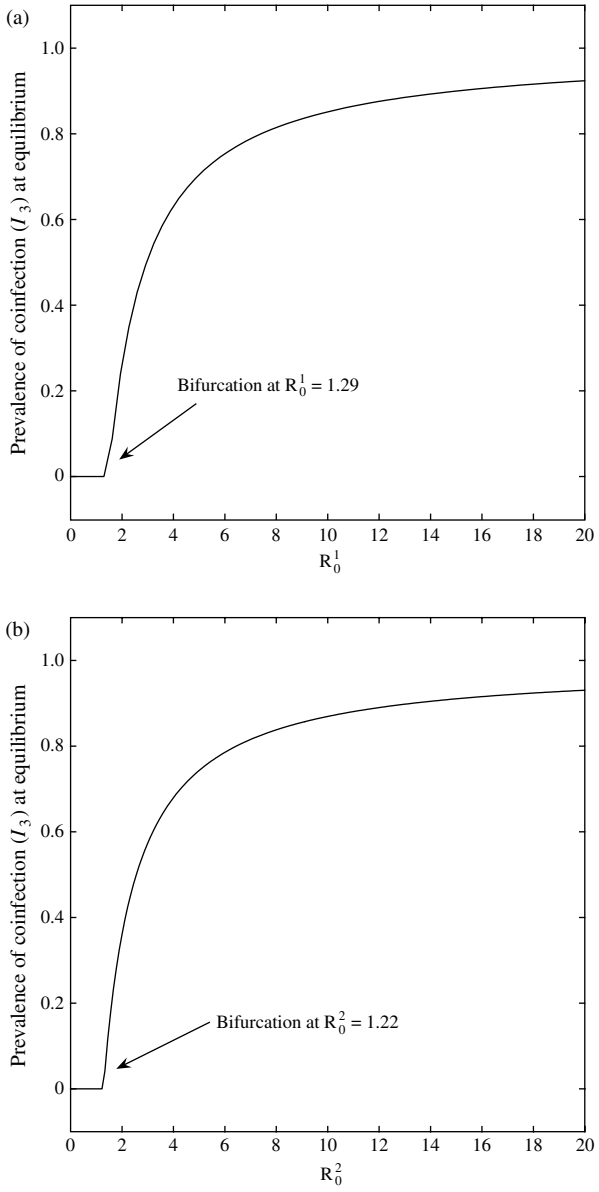
As with the QDFE, we can determine the local stability of the CIE. Due to the analytical complexity, we only evaluate the stability conditions in a numerical example.

2.3.4. Numerical Analysis of Equilibria. We performed equilibrium analysis for a numerical example in which $\mu_1 > 0$ and $\mu_2 > 0$ (Figure 2). We used demographic data for India ($N = 288{,}000{,}000$, $\Lambda = 0.022N$, $\mu = 0.016$), and chose the remaining parameters for two hypothetical diseases with low mortality ($\mu_1 = 0.005$, $\mu_2 = 0.01$) and reduced transmissibility ($\beta = 1$, $\tau = 2$). Under these assumptions, the DFE is locally unstable; the only possible stable equilibria are the QDFE and the CIE. For the given parameter values, we verify numerically that the CIE is stable. In terms of disease prevalence (i.e., the proportion of individuals in each compartment), the CIE is

$$\left(\frac{S^*}{N}, \frac{I_1^*}{N}, \frac{I_2^*}{N}, \frac{I_3^*}{N}\right) = (0.0077, 0.0038, 0.0153, 0.9732).$$

Figure 2 shows the prevalence of coinfected individuals (I_3/N) at equilibrium for different values of R_0^1

Figure 2. Prevalence of coinfected individuals, I_3, at equilibrium for different values of (a) disease 1 reproduction number (R_0^1), and (b) disease 2 reproduction number (R_0^2).



(Figure 2(a)) and R_0^2 (Figure 2(b)). For values of $R_0^1 < 1.29$, only disease 2 is present at equilibrium, and the second QDFE, E_2, is stable. For $R_0^1 > 1.29$, both diseases persist, leading to a co-infection equilibrium where $I_3 > 0$. Similarly, for $R_0^2 < 1.22$, the first QDFE, E_1, is stable, and for $R_0^2 > 1.22$, the CIE is stable.

For this example, we also compare the true CIE with the approximate CIE obtained using Equation (12), where we assume that $\mu_1 = \mu_2 = 0$. Disease prevalence at the approximate CIE is

$$\left(\frac{\hat{S}}{N}, \frac{\hat{I}_1}{N}, \frac{\hat{I}_2}{N}, \frac{\hat{I}_3}{N}\right) = (0.0054, 0.0026, 0.0106, 0.9814).$$

We observe that Equation (12) provides a reasonable approximation of the true CIE. The approximate CIE converges to the true CIE as the values of μ_1 and μ_2 approach zero.

3. SII × SEI Model

3.1. SII × SEI Model Formulation

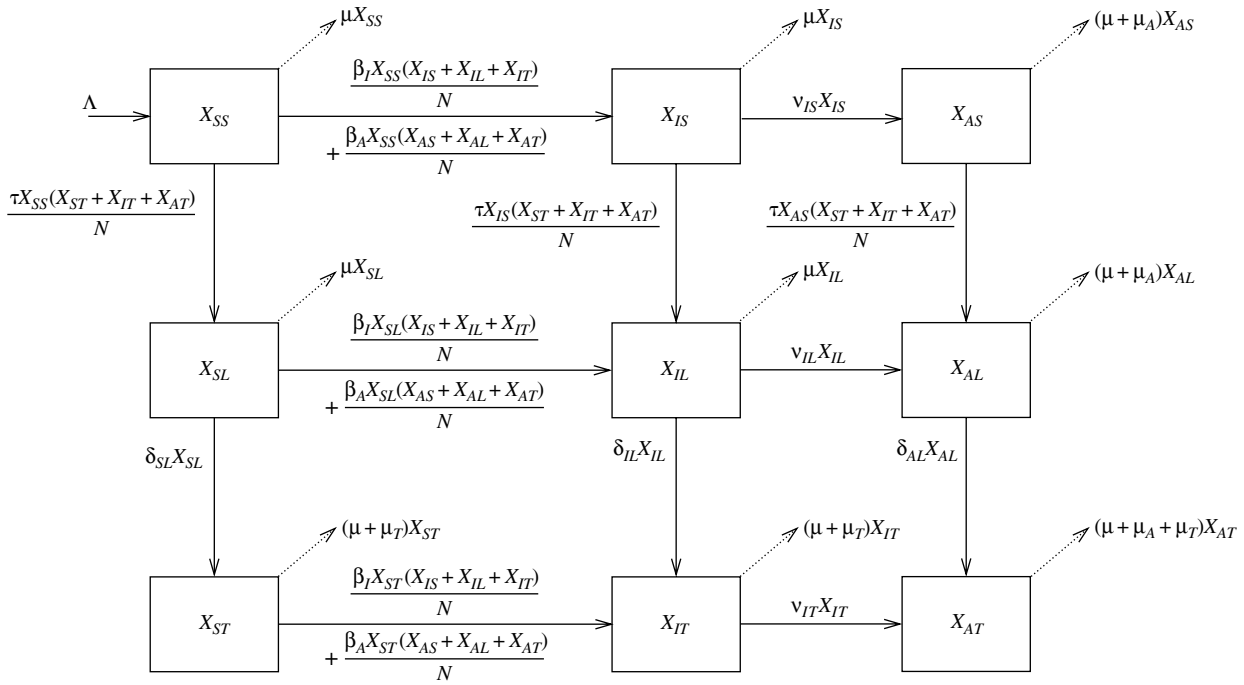
We now consider a model in which one disease has three states (susceptible, infected with no symptoms, and infected with symptoms), and the second disease has three different states (susceptible, exposed, and infected) (Figure 3). We refer to this structure as an SII × SEI model. We selected these particular disease states to reflect the HIV-TB co-epidemics, and we label the disease states accordingly. The first disease characterizes HIV, where the states are susceptible (S), infected with HIV but asymptomatic (I), and AIDS (A). We assume that the disease stage "AIDS" occurs at the onset of symptoms. The second disease represents TB, where the states are susceptible (S), latent tuberculosis (L), and active tuberculosis (T).

The population is divided into nine mutually exclusive, collectively exhaustive compartments: HIV-susceptible and TB-susceptible (X_{SS}); HIV-infected and TB-susceptible (X_{IS}); AIDS-infected and TB-susceptible (X_{AS}); HIV-susceptible and latent TB-infected (X_{SL}); HIV-infected and latent TB-infected (X_{IL}); AIDS-infected and latent TB-infected (X_{AL}); HIV-susceptible and active TB-infected (X_{ST}); HIV-infected and active TB-infected (X_{IT}); and AIDS-infected and active TB-infected (X_{AT}). This notation assigns the first subscript letter of each compartment name to an HIV state, and the second subscript letter to a TB state.

In addition to disease transmission, we now include disease progression, which means either transitioning from an asymptomatic state to a symptomatic state (e.g., HIV to AIDS), or from an exposed (noninfectious) state to an infectious state (e.g., latent TB to active TB). We denote the number of people in each compartment at time t by $X_{SS}(t)$, $X_{IS}(t)$, $X_{AS}(t)$, $X_{SL}(t)$, $X_{IL}(t)$, $X_{AL}(t)$, $X_{ST}(t)$, $X_{IT}(t)$, and $X_{AT}(t)$. The total population size at time t is $N(t) \equiv X_{SS}(t) + X_{IS}(t) + X_{AS}(t) + X_{SL}(t) + X_{IL}(t) + X_{AL}(t) + X_{ST}(t) + X_{IT}(t) + X_{AT}(t)$.

We assume that HIV can only be transmitted through sexual contact, and that individuals in both the asymptomatic (I) and symptomatic (A) compartments can transmit

Figure 3. Schematic diagram of the SII × SEI model.



Notes. The boxes represent cohorts of individuals and the arrows represent disease transmission, disease progression, maturation, or death. X_{SS} = susceptible to both diseases, X_{IS} = infected with HIV, X_{AS} = infected with AIDS, X_{SL} = infected with latent TB, X_{IL} = infected with HIV and latent TB, X_{AL} = infected with AIDS and latent TB, X_{ST} = infected with active TB, X_{IT} = infected with HIV and active TB, X_{AT} = infected with AIDS and active TB.

the disease to HIV-susceptible individuals. The HIV sufficient contact rate, β, is a function of the average number of sexual partners, n, the average condom usage rate, c, and infectivity (i.e., the probability per unprotected sexual partnership that an infected individual transmits the disease to a susceptible individual), θ, according to the formula: $\beta = n(1-c)\theta$. We allow the sufficient contact rate to vary between the asymptomatic (β_I) and symptomatic states (β_A) because studies of HIV suggest that sexual behavior patterns and infectivity change as HIV progresses to AIDS (AVERT.ORG 2006b, Basu et al. 2004, Chandrasekaran et al. 2006, NACO 2001, Sanders et al. 2005, Venkataramana and Sarada 2001, Zaric et al. 2000). The HIV disease progression rate, ν, may vary according to TB status ($\nu_{IS}, \nu_{IL}, \nu_{IT}$) because the presence of TB infection is thought to accelerate an individual's progression from HIV to AIDS (AVERT.ORG 2006a, WHO 2006c).

TB transmission occurs through airborne contact, and only those with active TB (T) can transmit the disease. Individuals with latent TB (L) have already contracted the disease, but they are not infectious. The TB sufficient contact rate, τ, does not vary according to HIV status; all individuals with active TB are assumed to be equally infectious. The TB disease progression rate, δ, may vary according to HIV status ($\delta_{SL}, \delta_{IL}, \delta_{AL}$) because HIV infection increases the likelihood of developing active TB.

We denote the population mortality rate by μ, the mortality rate from AIDS by μ_A, and the mortality rate from active TB by μ_T. We assume that only those individuals who are in an advanced disease stage can die from that disease. As before, we assume a constant rate of new entries into the population, Λ. We assume that all parameter values are nonnegative. Mathematically, we write the SII × SEI model as

$$\frac{dX_{SS}}{dt} = \Lambda - \beta_I(X_{IS}+X_{IL}+X_{IT})\frac{X_{SS}}{N} - \beta_A(X_{AS}+X_{AL}+X_{AT})\frac{X_{SS}}{N} - \tau(X_{ST}+X_{IT}+X_{AT})\frac{X_{SS}}{N} - \mu X_{SS}, \quad (13)$$

$$\frac{dX_{SL}}{dt} = \tau(X_{ST}+X_{IT}+X_{AT})\frac{X_{SS}}{N} - \beta_I(X_{IS}+X_{IL}+X_{IT})\frac{X_{SL}}{N} - \beta_A(X_{AS}+X_{AL}+X_{AT})\frac{X_{SL}}{N} - (\delta_{SL}+\mu)X_{SL}, \quad (14)$$

$$\frac{dX_{ST}}{dt} = \delta_{SL}X_{SL} - \beta_I(X_{IS}+X_{IL}+X_{IT})\frac{X_{ST}}{N} - \beta_A(X_{AS}+X_{AL}+X_{AT})\frac{X_{ST}}{N} - (\mu+\mu_T)X_{ST}, \quad (15)$$

$$\frac{dX_{IS}}{dt} = \beta_I(X_{IS}+X_{IL}+X_{IT})\frac{X_{SS}}{N} + \beta_A(X_{AS}+X_{AL}+X_{AT})\frac{X_{SS}}{N} - \tau(X_{ST}+X_{IT}+X_{AT})\frac{X_{IS}}{N} - (\nu_{IS}+\mu)X_{IS}, \quad (16)$$

$$\frac{dX_{IL}}{dt} = \beta_I(X_{IS}+X_{IL}+X_{IT})\frac{X_{SL}}{N} + \beta_A(X_{AS}+X_{AL}+X_{AT})\frac{X_{SL}}{N} + \tau(X_{ST}+X_{IT}+X_{AT})\frac{X_{IS}}{N} - (\delta_{IL}+\nu_{IL}+\mu)X_{IL}, \quad (17)$$

$$\frac{dX_{IT}}{dt} = \beta_I(X_{IS}+X_{IL}+X_{IT})\frac{X_{ST}}{N} + \beta_A(X_{AS}+X_{AL}+X_{AT})\frac{X_{ST}}{N} + \delta_{IL}X_{IL} - (\nu_{IT}+\mu+\mu_T)X_{IT}, \quad (18)$$

$$\frac{dX_{AS}}{dt} = \nu_{IS}X_{IS} - \tau(X_{ST}+X_{IT}+X_{AT})\frac{X_{AS}}{N} - (\mu+\mu_A)X_{AS}, \quad (19)$$

$$\frac{dX_{AL}}{dt} = \nu_{IL}X_{IL} + \tau(X_{ST}+X_{IT}+X_{AT})\frac{X_{AS}}{N} - (\delta_{AL}+\mu+\mu_A)X_{AL}, \quad (20)$$

$$\frac{dX_{AT}}{dt} = \nu_{IT}X_{IT} + \delta_{AL}X_{AL} - (\mu+\mu_A+\mu_T)X_{AT}. \quad (21)$$

We denote the compartment sizes in vector form as

$$(X_{SS}, X_{SL}, X_{ST}, X_{IS}, X_{IL}, X_{IT}, X_{AS}, X_{AL}, X_{AT}).$$

For the SII × SEI model, we calculate R_0 and determine the conditions under which the DFE is locally and globally stable. We calculate the QDFE, and show numerical conditions under which the CIE exists. We also extend the model to include treatment.

3.2. Basic Reproduction Number

We calculate R_0 for the system of Equations (13)–(21), using the next generation operator method (van den Driessche and Watmough 2002):

$$R_0 = \max\{R_0^H, R_0^T\}, \quad (22)$$

where

$$R_0^H = \frac{\beta_I}{\nu_{IS}+\mu} + \frac{\beta_A\nu_{IS}}{(\nu_{IS}+\mu)(\mu+\mu_A)},$$

$$R_0^T = \frac{\tau\delta_{SL}}{(\delta_{SL}+\mu)(\mu+\mu_T)}.$$

Suppose that a single-disease model (HIV-only) is constructed:

$$\frac{dX_{SS}}{dt} = \Lambda - \beta_I X_{IS}\frac{X_{SS}}{N} - \beta_A X_{AS}\frac{X_{SS}}{N} - \mu X_{SS},$$

$$\frac{dX_{IS}}{dt} = \beta_I X_{IS}\frac{X_{SS}}{N} + \beta_A X_{AS}\frac{X_{SS}}{N} - (\nu_{IS}+\mu)X_{IS},$$

$$\frac{dX_{AS}}{dt} = \nu_{IS}X_{IS} - (\mu+\mu_A)X_{AS},$$

$$N = X_{SS} + X_{IS} + X_{AS}.$$

Similarly, suppose that a TB-only model is constructed:

$$\frac{dX_{SS}}{dt} = \Lambda - \tau X_{ST}\frac{X_{SS}}{N} - \mu X_{SS},$$
$$\frac{dX_{SL}}{dt} = \tau X_{ST}\frac{X_{SS}}{N} - (\delta_{SL}+\mu)X_{SL},$$
$$\frac{dX_{ST}}{dt} = \delta_{SL}X_{SL} - (\mu+\mu_T)X_{ST},$$
$$N = X_{SS} + X_{SL} + X_{ST}.$$

As with the SI × SI model, the terms R_0^H and R_0^T (from the co-epidemic model) coincide with the single-disease basic reproduction numbers for HIV and TB, respectively. The terms R_0^H and R_0^T are not symmetric because HIV is modeled with an SII framework, and TB is modeled with an SEI framework.

3.3. SII × SEI Model Equilibria Analysis

3.3.1. Disease-Free Equilibrium (DFE). The DFE of the system of Equations (13)–(21) is

$$E_0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0, 0, 0, 0\right). \tag{23}$$

The condition for local asymptotic stability of the disease-free equilibrium in the SI × SI model (Proposition 1) also holds for the SII × SEI model. To establish global stability, we use a modified Lyapunov function: $L = (\mu/2)(X_{SS} - \Lambda/\mu)^2 + \Lambda(X_{SL} + X_{ST} + X_{IS} + X_{IL} + X_{IT} + X_{AS} + X_{AL} + X_{AT})$.

Proposition 5 (Global Stability of DFE in the SII × SEI Model). *Suppose that*

$$\max\left\{\frac{\beta_I}{\mu}, \frac{\beta_I+\tau}{\mu+\mu_T}, \frac{\beta_A}{\mu+\mu_A}, \frac{\beta_A+\tau}{\mu+\mu_A+\mu_T}\right\} < \frac{1}{2}. \tag{24}$$

Then, the DFE, E_0, is globally asymptotically stable.

In Equation (24), each term corresponds to a compartment with individuals infected with one or both diseases. Once again, the numerator in each term represents the force of infection and the denominator represents the removal rate of infected individuals.

3.3.2. Quasi-Disease-Free Equilibria (QDFE).

HIV-Only QDFE. For the first QDFE, only HIV is present:

$$E_1 = (\widehat{X}_{SS}, 0, 0, \widehat{X}_{IS}, 0, 0, \widehat{X}_{AS}, 0, 0), \tag{25}$$

where

$$\widehat{X}_{SS} = \frac{\Lambda(\nu_{IS}+\mu+\mu_A)}{\beta_I(\mu_A+\mu)+\nu_{IS}(\beta_A-\mu_A)},$$
$$\widehat{X}_{IS} = \frac{\Lambda(\mu+\mu_A)(R_0^H-1)}{\beta_I(\mu_A+\mu)+\nu_{IS}(\beta_A-\mu_A)},$$
$$\widehat{X}_{AS} = \frac{\Lambda\nu_{IS}(R_0^H-1)}{\beta_I(\mu_A+\mu)+\nu_{IS}(\beta_A-\mu_A)}.$$

E_1 exists if $R_0^H > 1$.

TB-Only QDFE. Conversely, for the second QDFE, only TB is present:

$$E_2 = (\widehat{X}_{SS}, \widehat{X}_{SL}, \widehat{X}_{ST}, 0, 0, 0, 0, 0, 0), \tag{26}$$

where

$$\widehat{X}_{SS} = \frac{\Lambda(\delta_{SL}+\mu+\mu_T)}{\delta_{SL}(\tau-\mu_T)},$$
$$\widehat{X}_{SL} = \frac{\Lambda(\mu+\mu_T)(R_0^T-1)}{\delta_{SL}(\tau-\mu_T)},$$
$$\widehat{X}_{ST} = \frac{\Lambda(R_0^T-1)}{\tau-\mu_T}.$$

E_2 exists if $R_0^T > 1$.

Due to the analytical complexity of the nine-dimensional SII × SEI model, we do not include stability analysis of the QDFE.

3.3.3. Co-Infection Equilibrium (CIE). At the CIE, at least one co-infection compartment must be nonempty: $X_{IL} + X_{AL} + X_{IT} + X_{AT} > 0$. The CIE is found by setting the system of Equations (13)–(21) equal to zero and solving. Due to the size and nonlinear complexity of the SII × SEI model, an analytical solution for the CIE cannot be obtained. In §4, using an illustrative example of the HIV-TB co-epidemic in India, we calculate the numerical threshold for the CIE.

3.4. SII × SEI Model with Treatment

We now extend the SII × SEI model to include treatment. We assume that treatment extends an individual's life and reduces that person's chance of infecting others (by reducing infectivity). We assume that all individuals receive the same treatment and have the same average response to treatment. We recognize that treatment for HIV and TB often involves individualized regimens that cannot be appropriately captured with a simple compartmental model. We ignore additional complexity associated with treatment, such as toxicity and drug resistance.

Current treatment for HIV is known as highly active antiretroviral therapy (HAART). We assume that only individuals with AIDS (those in compartments X_{AS}, X_{AL}, and X_{AT}) are eligible to receive HAART, consistent with treatment guidelines established by the World Health Organization (WHO 2006a). HAART significantly increases an individual's life expectancy, which decreases the AIDS-related death rate (μ_A); and HAART decreases an individual's viral load, which reduces the transmission probability (θ_A), and consequently the sufficient contact rate (β_A). We assume that HAART has no effect on sexual behavior.

Individuals with latent TB can be given isoniazid preventive therapy (IPT) to eliminate the chance of developing active TB and reduce the TB progression rates (δ_{SL}, δ_{IL}, δ_{AL}). IPT also reduces the AIDS progression rate (ν_{IL})

in individuals coinfected with HIV. Active TB is treated with a longer course of antibiotics and provides several benefits: treatment reduces an individual's rate of progression from HIV to AIDS (ν_{IT}); treated individuals cannot infect others, which reduces the sufficient contact rate (τ); and mortality from active TB (μ_T) is reduced.

The system of equations and equilibrium formulas for the SII × SEI model with treatment is virtually the same as without treatment, except that the parameters mentioned above (μ_A, μ_T, θ_A, β_A, τ, ν_{IL}, ν_{IT}, δ_{SL}, δ_{IL}, δ_{AL}) are now indexed over treatment levels.

4. HIV-TB in India: Illustrative Numerical Analysis

4.1. Overview

We applied our SII × SEI model with treatment to perform an illustrative numerical analysis of the HIV-TB co-epidemics in India. We examined hypothetical treatment and prevention scenarios to gain insight into the underlying co-epidemic dynamics. We considered nine treatment scenarios: no treatment, 50% HAART, 100% HAART, 50% latent TB treatment, 100% latent TB treatment, 50% active TB treatment, 100% active TB treatment, 50% combination treatment, and 100% combination treatment, where the % denotes the fraction of the eligible population receiving the corresponding treatment, and combination treatment includes all three treatments. We also considered the effect of seven prevention scenarios: no prevention; moderate increase in condom use; significant increase in condom use; moderate reduction in TB contact rate; significant reduction in TB contact rate; moderate increase in condom use and moderate reduction in TB contact rate; and significant increase in condom use and significant reduction in TB contact rate. For all numerical analyses, we used a 20-year time horizon and we estimated disease prevalence, the number of new cases of HIV, latent TB, and active TB, and total disease-related deaths.

In a separate numerical analysis, we calculated R_0 under different treatment and prevention scenarios. Specifically, we considered treatment of each disease ranging from 0%–100% treatment coverage in the population, and we considered changes in the average rate of condom use (c) and the active TB sufficient contact rate (τ). We also performed one-way sensitivity analysis to determine the effect of key model parameters on R_0.

Finally, we compared the numerical results from the SII × SEI model to those obtained using two single-disease models.

4.2. Data and Assumptions

We included the entire population in the southern states of Maharashtra, Andhra Pradesh, Karnataka, and Tamil Nadu (approximately 288 million people) because of the relatively high prevalence of HIV in these regions and lack of universal access to treatment. Average HIV prevalence in these states is 1.3% (AVERT.ORG 2006c), and only 5% of those in need of HAART received treatment in 2005 (WHO 2005). TB remains a significant health problem throughout the country; India accounts for one-fifth of all TB cases worldwide (Dye 2006). Despite improved access to treatment, only 50% of new active TB cases in India were successfully treated in 2004 (Dye 2006), and virtually no people received latent TB prophylaxis. However, increased HIV and active TB treatment, along with improved case detection, are expected in the near future.

We estimated demographic and disease parameters for the model based on a review of the literature (Table 1). We assumed a linear relationship between treatment levels and the associated parameters.

4.3. Disease Outcomes: Prevalence and New Infections

For each hypothetical treatment and prevention scenario, we estimated the number of new cases of HIV, latent TB, and active TB, as well as HIV- and TB-related deaths over the 20-year time horizon (Table 2).

4.3.1. Base Case. Figure 4 shows estimated disease prevalence over time in the absence of any prevention or treatment programs. HIV prevalence reached 3.7% after 20 years, a substantial increase from the current level of 1.3%; latent TB prevalence increased from 40% to 52.5% after 20 years; and active TB prevalence increased from 0.7% to 1% after 20 years.

4.3.2. Effect of Single Treatment on Disease Outcomes. We considered the effect of each type of treatment in isolation (e.g., HAART for individuals with AIDS, but no treatment for latent or active TB). The provision of HAART significantly slowed the HIV epidemic (Figure 5(a)). With 50% coverage, an estimated 3 million HIV infections were prevented over 20 years, whereas 100% coverage prevented almost 10 million HIV infections, compared to no treatment. However, exclusively treating HIV-infected individuals with HAART adversely affected the TB epidemic (Figure 5(a)). Because HAART reduces AIDS-related mortality, treated individuals have a longer time to potentially infect others with TB, especially in the absence of any TB treatment. Thus, the numbers of new latent and active TB cases increased as more people were given HAART. HAART also significantly decreased disease-related deaths: with 50% HAART coverage, 2.3 million fewer people died from HIV or TB over 20 years, and with 100% HAART coverage, 7.3 million fewer deaths occurred (Table 2).

Exclusively treating people with latent TB reduced the number of new active TB cases, which subsequently decreased the number of new latent TB infections (Figure 5(b)). However, latent TB treatment had an adverse effect on the HIV epidemic: the number of new HIV cases increased because individuals coinfected with HIV and

Table 1. HIV-TB model parameters for the case of no treatment or prevention.[a]

Description	Parameter	Base value [low-high]	Source
Demographic parameters			
Total population	N	288,000,000	(AVERT.ORG 2006c, Registrar of India 2001, WHO 2006c, WHO 2006e)
Initial compartments			
No HIV, No TB	$X_{SS}(0)$	168,558,250	Calculated
No HIV, Latent TB	$X_{SL}(0)$	113,718,000	Calculated
No HIV, Active TB	$X_{ST}(0)$	2,018,750	Calculated
HIV+, No TB	$X_{IS}(0)$	1,587,563	Calculated
HIV+, Latent TB	$X_{IL}(0)$	1,111,500	Calculated
HIV+, Active TB	$X_{IT}(0)$	79,687	Calculated
AIDS, No TB	$X_{AS}(0)$	529,188	Calculated
AIDS, Latent TB	$X_{AL}(0)$	370,500	Calculated
AIDS, Active TB	$X_{AT}(0)$	26,562	Calculated
Maturation	Λ	$0.022 \times N$	(U.S. CIA 2006)
Death rate (non-HIV/TB)	μ	0.016	(WHO 2006b)
HIV disease parameters			
Sufficient contact rate			
HIV	β_I	0.170	Calculated
AIDS	β_A	0.204	Calculated
HIV progression rate			
No TB	ν_{IS}	0.085 [0.01–0.2]	(Zaric et al. 2000)
Coinfected with LTB	ν_{IL}	0.17 [0.085–0.5]	Estimated
Coinfected with ATB	ν_{IT}	1	Estimated
AIDS death rate	μ_A	0.5 [0.25–0.9]	(Walensky et al. 2006, Zaric et al. 2000)
TB disease parameters			
Sufficient contact rate			
Active TB	τ	4 [2–10]	(Sanchez and Blower 1997, WHO 2006e, Ziv et al. 2001)
TB progression rate			
No HIV	δ_{SL}	0.0038 [0.001–0.01]	(Sanchez and Blower 1997, WHO 2006c, WHO 2006e)
Coinfected with HIV	δ_{IL}	0.05 [0.01–0.1]	Estimated (WHO 2006c, WHO 2006e)
Coinfected with AIDS	δ_{AL}	0.1 [0.05–0.2]	Estimated (WHO 2006c, WHO 2006e)
Active TB death rate	μ_T	0.2 [0.1–0.3]	(Atun et al. 2005, Sanchez and Blower 1997, WHO 2006c)
Sexual behavior parameters			
Annual no. of sex partners			
Individual with HIV	n_I	5 [1–10]	Estimated (NACO 2001)
Individual with AIDS	n_A	3 [0.5–6]	Estimated
Condom use	c	0.15 [0.05–0.5]	Estimated (AVERT.ORG 2006b, Basu et al. 2004, Chandrasekaran et al. 2006, Venkataramana and Sarada 2001)
Prob. of HIV transmission			
Sex partner with HIV	θ_I	0.04 [0.01–0.06]	(Sanders et al. 2005, Zaric et al. 2000)
Sex partner with AIDS	θ_A	0.08 [0.05–0.11]	(Sanders et al. 2005, Zaric et al. 2000)

Notes. With 100% HIV treatment: $\beta_A = 0.020$, $\mu_A = 0.067$, $\theta_A = 0.008$.
With 100% latent TB treatment: $\nu_{IL} = 0.085$, $\delta_{SL} = \delta_{IL} = \delta_{AL} = 0$.
With 100% active TB treatment: $\nu_{IT} = 0.170$, $\tau = 0$, $\mu_T = 0$.
With 50% treatment, the corresponding parameters are the average of no treatment and 100% treatment.
[a]HIV = human immunodeficiency virus, TB = tuberculosis, LTB = latent tuberculosis, ATB = active tuberculosis.

latent TB lived longer (due to latent TB treatment) and thus could infect more people with HIV.

Similarly, active TB treatment reduced the number of people with infectious TB, which subsequently reduced the number of new latent and active TB cases (Figure 5(c)). Once again, new HIV cases increased due to longer life expectancy among those who were coinfected with HIV.

4.3.3. Effect of Joint Treatment on Disease Outcomes. We evaluated the effect of providing universal treatment

Table 2. Number of new HIV cases, latent TB cases, active TB cases, and total disease-related deaths over 20 years under different treatment and prevention scenarios.[a]

Treatment or prevention scenario	New HIV cases (millions)	New LTB cases (millions)	New ATB cases (millions)	Disease-related deaths (millions)
No treatment or prevention	22.91	104.48	13.55	22.36
50% HIV treatment	19.90	107.64	13.85	20.08
100% HIV treatment	13.27	115.19	14.47	15.10
50% LTB treatment	26.85	65.86	6.53	18.19
100% LTB treatment	32.04	22.25	0.00	14.12
50% ATB treatment	24.28	78.46	12.33	19.67
100% ATB treatment	27.61	0.00	9.18	12.93
50% all treatment	24.51	51.83	6.23	14.49
100% all treatment	21.88	0.00	0.00	4.25
Increased condom use				
$c = 0.30$	13.02	102.20	12.52	18.55
$c = 0.60$	3.84	99.78	11.46	14.43
Reduced TB contact				
$\tau = 2$	23.91	53.25	11.38	21.02
$\tau = 1$	24.44	26.40	10.23	20.31
Increased condom use and reduced TB contact				
$c = 0.30$, $\tau = 2$	13.55	52.05	10.55	17.35
$c = 0.60$, $\tau = 1$	4.02	25.22	8.79	12.80

Notes. HIV = human immunodeficiency virus, TB = tuberculosis, LTB = latent tuberculosis, ATB = active tuberculosis.

c = average condom use, τ = active TB sufficient contact rate. With no treatment or prevention, $c = 0.15$ and $\tau = 4$.

[a]Disease-related deaths are total deaths due to HIV or TB over 20 years.

for HIV, latent TB, and active TB. Treating 100% of eligible, infected individuals (i.e., those infected with HIV, TB, or both) increased HIV prevalence from the current level of 1.3% to almost 6% after 20 years. Treatment increases an individual's life expectancy, which can increase HIV prevalence for two reasons: (1) individuals with HIV live longer and are thus included in the estimates of HIV prevalence, and (2) these individuals can infect more people, despite a significant reduction in infectivity. Conversely, universal treatment decreased latent TB prevalence from 40% to 26.2% and active TB prevalence from 0.7% to 0.5% after 20 years. Universal treatment for HIV, latent TB, and active TB prevented more than 1 million new HIV infections, 104 million new latent TB infections, and 14 million new active TB cases over 20 years (Table 2). Additionally, 18 million HIV- or TB-related deaths were avoided over 20 years (Table 2).

The opposite effects of universal treatment on HIV and TB prevalence emphasize the difference between each disease's transmission dynamics. Providing HAART to HIV-infected individuals significantly increases life expectancy (μ_A decreases); however, they can potentially infect others even though their infectivity (β_A) decreases. Even with universal treatment, the HIV epidemic was not diminished, for two reasons: (1) people with asymptomatic HIV were not eligible to receive HAART, and (2) individuals with AIDS who were given HAART could still transmit the virus to others. On the other hand, treating people with active TB extends their life expectancy (μ_T decreases), but they are no longer infectious (τ decreases to zero). The TB epidemic could be reduced through universal treatment because: (1) everyone with latent or active TB was eligible to receive treatment, and (2) active TB treatment eliminated the chance of infecting others.

4.3.4. Effect of Prevention on Disease Outcomes. We evaluated the effects of two illustrative prevention programs: one that increases condom use (c) and one that reduces the active TB contact rate (τ). Changes in these parameters could occur due to behavioral interventions: varying condom use is similar to varying the number of sexual partners (e.g., doubling condom use is equivalent to halving the number of sexual partners); varying the active TB contact rate could account for decreased contact between susceptible and infected individuals (e.g., using face masks to prevent airborne transmission of TB).

If average condom use increased from a current level of $c = 0.15$ to $c = 0.30$, HIV prevalence reached 1.9% after 20 years (compared to 3.7% in the base case), and almost 10 million HIV infections were prevented (Table 2).

Figure 4. Projected prevalence of HIV, latent TB, and active TB over time using a co-epidemic model (HIV and TB) vs. single-disease models (HIV only or TB only).

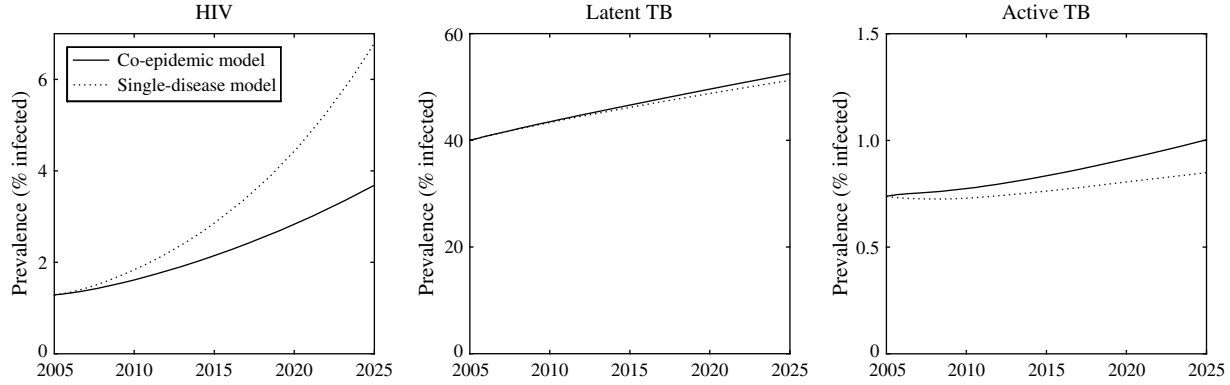
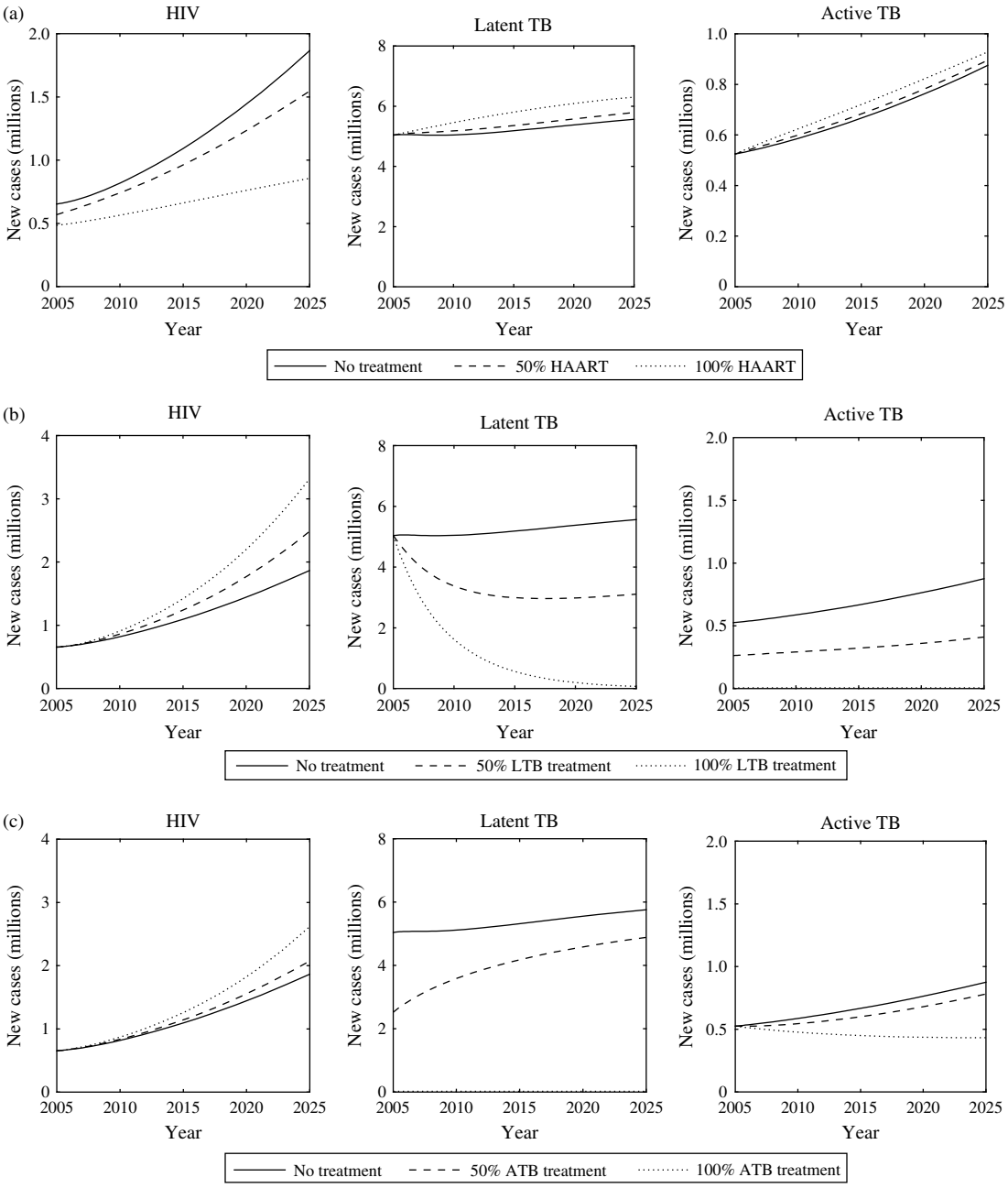


Figure 5. Number of new HIV infections, latent TB infections, and active TB cases over time under different (a) HIV treatment scenarios, (b) latent TB treatment scenarios, and (c) active TB treatment scenarios.



Notes. HAART = highly active antiretroviral therapy, LTB = latent tuberculosis, ATB = active tuberculosis.

If average condom use increased further to $c = 0.60$, HIV prevalence *decreased* to 0.5% after 20 years, and 19 million HIV infections were prevented.

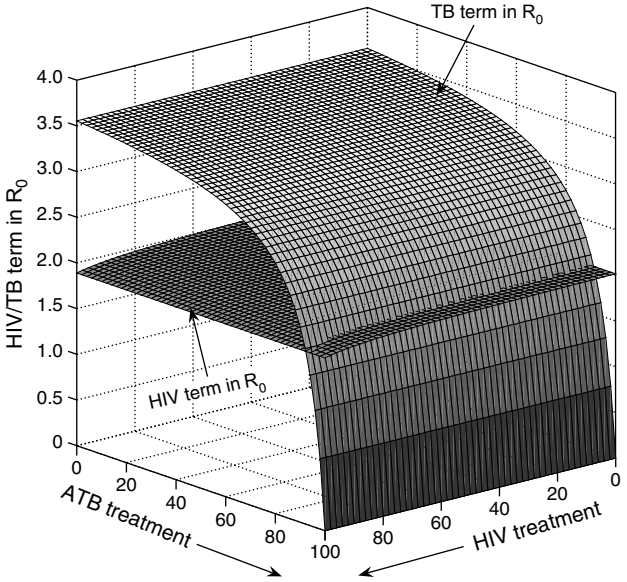
If the active TB contact rate decreased from $\tau = 4$ to $\tau = 2$, then latent TB and active TB prevalences remained relatively constant over 20 years (instead of increasing, as in the base case). Under this scenario, more than 50 million latent TB infections and 2 million active TB cases were averted over 20 years. If the contact rate was reduced to $\tau = 1$, then latent TB prevalence decreased to 31%, active TB prevalence decreased slightly to 0.6%, and 78 million latent TB infections and 3 million active TB cases were prevented.

If condom use increased and the active TB contact rate decreased, the benefits were approximately additive. Moreover, HIV- and TB-related deaths significantly decreased (Table 2).

4.4. Reproductive Rate of Infection

In addition to estimating population and disease outcomes for various treatment and prevention scenarios, we determined the conditions under which R_0 was less than one.

Figure 6. 3-D plot showing the effects of HIV treatment and active TB treatment on the HIV reproduction number (R_0^H) and the TB reproduction number (R_0^T).



Note. ATB = active tuberculosis.

4.4.1. Effect of Treatment on R_0. Figure 6 shows the effect of different HIV and active TB treatment levels on R_0. Under the base-case assumption of no treatment, $R_0 = \max\{R_0^H, R_0^T\} = 3.55$. With no HIV treatment, $R_0^H = 2.02$; with 100% treatment coverage, $R_0^H = 1.89$. R_0^H only moderately decreased because individuals with asymptomatic HIV were not eligible to receive HAART, and those undergoing HAART could still infect others. With no active TB treatment, $R_0^T = 3.55$; this decreased to $R_0^T = 0$ with 100% active TB treatment coverage because treated individuals could no longer infect others.

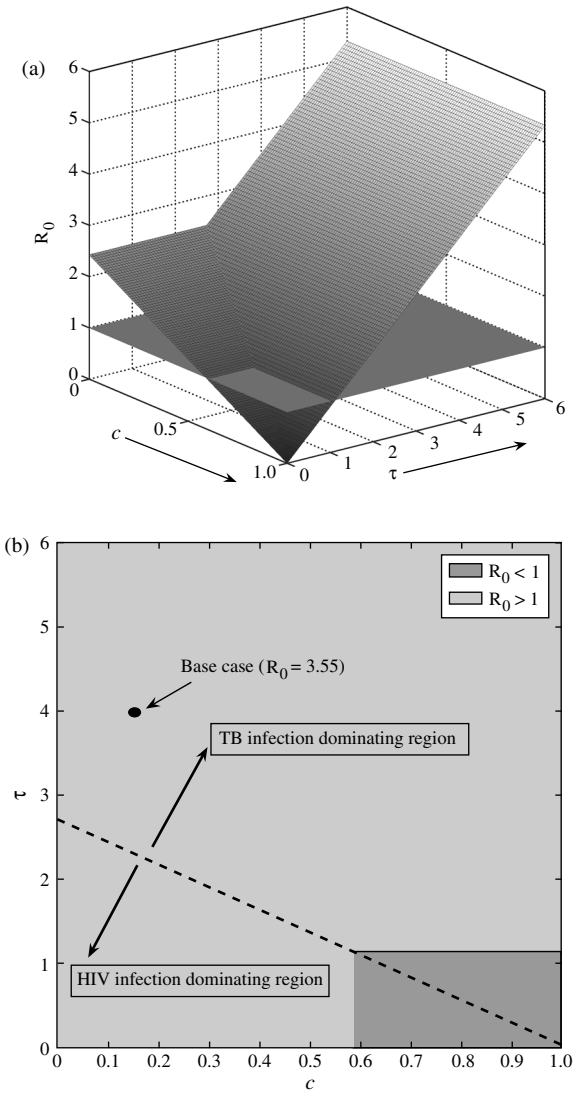
Although not shown, we also considered the effect of latent TB treatment on R_0. Latent TB treatment decreases an infected individual's chance of developing active TB ($\delta_{SL}, \delta_{IL}, \delta_{AL}$ decrease to zero). After examining the TB reproduction number,

$$R_0^T = \frac{\tau\delta_{SL}}{(\delta_{SL}+\mu)(\mu+\mu_T)},$$

we note that identical percentage reductions in τ or δ_{SL} will have similar effects on R_0^T (changes in δ_{SL} are negligible in the denominator because the μ term dominates δ_{SL}). Because of this symmetry, we only show the effect of joint HIV treatment and active TB treatment on R_0 (Figure 6).

4.4.2. Effect of Prevention on R_0. To determine the effects of disease prevention on R_0, we calculated R_0 as a function of the condom usage rate (c) and the active TB sufficient contact rate (τ) (Figure 7). For values of $\tau > 2.67$ (base-case estimate: $\tau = 4$), R_0^T dominated R_0^H for all values

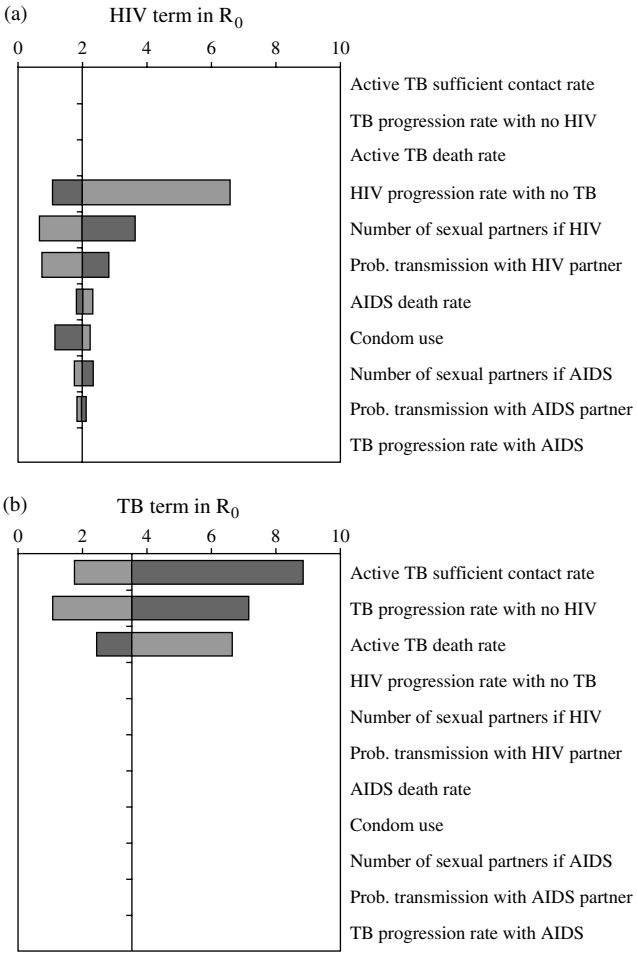
Figure 7. (a) 3-D plot and (b) contour plot showing the effects of average condom use (c) and the active TB sufficient contact rate (τ) on the basic reproduction number (R_0).



of c. For values of $\tau < 2.67$, either R_0^H or R_0^T could dominate, depending on values of τ and c: R_0^H and R_0^T are equal if $\tau = 2.67 - 2.67c$; R_0^T dominated if $\tau > 2.67 - 2.67c$; R_0^H dominated if $\tau < 2.67 - 2.67c$ (Figure 7). If $\tau < 1.125$ and $c > 0.578$, then $R_0 < 1$. This numerical analysis suggests that if prevention programs sufficiently reduce τ and increase c, the HIV-TB co-epidemics could theoretically be eradicated. Figure 7(b) shows a cross-section of Figure 7(a) along the contour $R_0 = 1$, and illustrates which values of c and τ will lead to $R_0 < 1$.

4.4.3. Sensitivity Analysis. We performed one-way sensitivity analysis to determine the effect of key model parameters on R_0 (Figure 8). We allowed each parameter to take on the low and high value shown in Table 1. The key parameters influencing R_0^H include the HIV progres-

Figure 8. Sensitivity analysis of model parameters to the (a) HIV reproduction number (R_0^H), and (b) TB reproduction number (R_0^T).



Notes. The basic reproduction number (R_0) is the maximum of R_0^H and R_0^T. The vertical axis in each graph corresponds to the base case with no treatment, where $R_0^H = 2.02$ and $R_0^T = 3.55$. The horizontal bars illustrate the change in R_0^H or R_0^T as each parameter is varied. The black bar corresponds to a parameter taking on its high value, and the gray bar corresponds to a parameter taking on its low value.

sion rate with no TB (ν_{IS}), the average number of sexual partners of people with HIV (n_I), and the probability of disease transmission from an HIV-infected sexual partner (θ_I) (Figure 8(a)). The key parameters affecting R_0^T include the active TB sufficient contact rate (τ), the TB progression rate with no HIV (δ_{SL}), and the active TB death rate (μ_T) (Figure 8(b)). Over the range of values considered, R_0 reached a maximum of 8.89 and a minimum of 2.01, compared to the base-case value of 3.55.

4.5. Numerical Analysis of Equilibria

We analyzed the co-infection prevalence ($(X_{IL} + X_{AL} + X_{IT} + X_{AT})/N$) for different values of R_0^H and R_0^T. The system eventually stabilizes at the DFE (neither disease exists), the HIV-only QDFE, the TB-only QDFE, or the CIE (both diseases exist). In the base case, $R_0^H = 2.02$ and $R_0^T = 3.55$, so the DFE is locally unstable, and only the CIE or QDFE can be stable. If the HIV reproduction number decreases ($R_0^H < 1.541$), perhaps due to disease prevention measures, the system stabilizes at the TB-only QDFE. Similarly, for smaller values of the TB reproduction number ($R_0^T < 1.199$), the HIV-only QDFE persists. Above these thresholds, the CIE exists, and co-infection prevalence increases as R_0^H or R_0^T increase. The general shape of the bifurcation figure for this example is similar to that for the SI × SI model (Figure 2).

4.6. Co-Epidemic vs. Single-Disease Models

Prior studies of the HIV-TB co-epidemics have shown a strong relationship between the presence of one disease and the transmission and progression of the other disease (e.g., West and Thompson 1997, Porco et al. 2001, Currie et al. 2003, Williams et al. 2005, Dye et al. 1998, Dowdy et al. 2006, Corbett et al. 2006, Cohen et al. 2006). We removed selected compartments in our SII × SEI to show numerically how ignoring this synergistic dependence can influence disease outcomes.

We compared the numerical results from the co-epidemic model to results obtained using two single-disease models. Using the HIV-TB data for India (Table 1), we set initial HIV prevalence to 1.3%, latent TB prevalence to 40%, and active TB prevalence to 0.7%. With the co-epidemic model, prevalence reached 3.7% (HIV), 52.5% (latent TB), and 1% (active TB) after 20 years (Figure 4), resulting in 22.9 million (HIV), 104.5 million (latent TB), and 13.6 million (active TB) new infections over 20 years. When we independently simulated the diseases, prevalence reached 6.5% (HIV), 51.2% (latent TB), and 0.9% (active TB) after 20 years (Figure 4), and 32.7 million (HIV), 98.0 million (latent TB), and 10.5 million (active TB) new infections occurred.

HIV prevalence and incidence were higher when we ignored TB co-infection than with the co-epidemic model. TB is a common opportunistic infection and a leading cause of death among HIV-infected individuals. Excluding TB co-infection allows HIV-infected individuals to develop AIDS at a slower rate and survive for a longer period of time, which leads to higher HIV prevalence and a greater number of new HIV infections.

When we modeled TB independently, we obtained estimates of latent and active TB prevalence that were very similar to our estimates from the co-epidemic model. Although HIV co-infection increases the probability that an individual with latent TB develops active TB, the overall rate of developing active TB is quite small. However, when TB prevalence is estimated over a longer time horizon (e.g., 50 years), the effect of excluding HIV is more pronounced.

The differences between the co-epidemic and single-disease models depended on treatment coverage. The single-disease TB model underestimated the number of new

active TB cases by 1.9 million to 3.1 million cases, depending on active TB treatment coverage levels. Conversely, the level of HIV treatment did not significantly affect the difference in new HIV cases estimated by the single-disease HIV model versus the co-epidemic model.

5. Discussion

We have developed two mathematical models for modeling co-epidemics, an SI × SI model and an SII × SEI model. For both models, we calculated the basic reproduction number, the disease-free equilibrium, the quasi-disease-free equilibria (defined as a state where one disease is eradicated, whereas the other disease remains endemic), and conditions for local and global stability. For the SI × SI model, we determined the co-infection equilibrium for the special case where disease mortality is approximately zero. For both the SI × SI model and the SII × SEI model with nonzero disease mortality, our numerical analyses indicate that the CIE is stable for sufficiently high disease contact rates. The system stabilizes at a QDFE if the contact rate for one disease is below a threshold, and the DFE is stable if both contact rates are below particular thresholds. Our asymmetric SII × SEI model represents a novel approach that offers insight into co-epidemic dynamics and the effect of disease treatment and prevention on R_0 and equilibria stability.

Our numerical analysis of the HIV-TB co-epidemics in India produced several interesting observations. First, our analyses suggest that exclusive treatment of only one disease may substantially reduce that epidemic by decreasing disease prevalence and preventing new infections or deaths, but may exacerbate the other epidemic. This paradoxical result occurs because people treated for the first disease but coinfected with the second disease may live longer due to treatment, and subsequently may infect more people with the second disease.

This observation is consistent with findings from prior studies. Williams et al. (2005) observed that antiretroviral therapy for HIV would significantly reduce mortality in coinfected individuals, but would likely not decrease TB incidence, and that India's national TB treatment program could reverse the recent increase in TB incidence and reduce TB prevalence by 50%. Cohen et al. (2006, p. 7044) found that "although ARVs immediately reduced HIV-related deaths, they had minimal additional short-term effect on the prevalence of latent and active TB or measures of drug resistance." The authors showed that latent TB prophylaxis increased life expectancy in HIV-infected individuals, which increased HIV prevalence and provided a longer opportunity for these individuals to infect others with HIV. Currie et al. (2003) discussed how reducing HIV transmission would likely have a smaller effect on decreasing TB incidence than would provision of active TB treatment. The authors also found that latent TB prophylaxis was "comparatively ineffective" at reducing new TB cases, whereas our results suggest that this form of treatment significantly reduces new active TB cases. However, Currie et al. (2003) only considered treatment of latent TB in individuals coinfected with HIV, whereas we included treatment of all individuals with latent TB.

Second, our numerical analyses suggest that prevention plays an important role in slowing the spread of HIV and TB. Even with 100% treatment of HIV and TB, R_0 remains greater than one. Our numerical results indicate that to reduce R_0 below one and diminish both epidemics, it is necessary to include HIV and TB prevention programs.

Third, our analyses highlight the importance of including the effects of HIV on the TB epidemic, and vice versa. We compared disease outcomes with the co-epidemic model versus single-disease models. Our results suggest that ignoring co-infection leads to significantly higher estimates of HIV prevalence and incidence, but this difference is not sensitive to the fraction of individuals receiving HIV treatment. Conversely, TB prevalence and incidence levels are relatively similar with the co-epidemic and single-disease models. However, this difference is sensitive to TB treatment levels: low treatment levels magnify the difference, and high treatment levels diminish this effect.

Our third finding is consistent with a prior study by Porco et al. (2001), who showed that HIV significantly exacerbates the magnitude and frequency of TB outbreaks, and this amplification effect depends on the level of TB treatment. If TB treatment levels are low or moderate, an HIV epidemic could double the size of a TB epidemic, whereas if TB treatment levels are high, the effect of HIV on the TB epidemic is minimal.

Our models have several limitations. We simplified the complicated infection dynamics of HIV and TB to develop a tractable analytical framework, which helped us gain insights about the basic reproduction number and disease equilibria. We assumed uniform behavior patterns within compartments and homogeneous mixing between compartments. We assumed that all individuals in a particular compartment have identical infectivity, which is unlikely because diseases such as HIV and TB typically progress through a continuum of disease states. Finally, limited data exists on the interaction of HIV and TB; thus, our numerical estimates of model parameters relied on upper and lower bounds found in the literature. To appropriately guide policy recommendations, our co-epidemic model would need to be significantly expanded.

Our methodology for modeling co-epidemics can be used to extend single-disease models that include varying degrees of complexity, such as stages of infectivity, exposed classes, recovery, and age structure, as well as interventions such as treatment, isolation, and quarantine. We could apply a co-epidemic model to other diseases, such as HIV and hepatitis C (HCV). Some 50%–90% of HIV-infected injection drug users are coinfected with HCV (CDC 2005). HIV treatment success may be adversely affected by the presence of HCV, and HCV may cause liver

damage to occur more quickly in HIV-infected individuals (CDC 2005). Modeling this co-infection may be particularly important to consider when evaluating interventions targeted to injection drug using populations.

Mathematical models can help guide policymakers in allocating resources for the prevention and control of infectious disease epidemics. Our numerical analyses of the HIV-TB co-epidemics suggest that exclusive treatment of only one disease may substantially reduce that epidemic, but may exacerbate the other epidemic; that prevention programs can have a greater effect on reducing R_0 than treatment alone; and that comprehensive treatment for HIV, latent TB, and active TB must be combined with increased prevention efforts to reduce R_0 below one and diminish both epidemics. Finally, when modeling two or more synergistic infectious disease epidemics, it is important to include the effects of each disease on the transmission and progression of the other disease.

6. Electronic Companion

An electronic companion to this paper is available as part of the online version that can be found at http://or.journal.informs.org/.

Acknowledgments

This work was supported by a grant (R-01-DA-15612) from the National Institute on Drug Abuse; the Seth Bonder Scholarship for Applied Operations Research in Health Services, sponsored by the Institute for Operations Research and the Management Sciences (INFORMS); the Natural Science and Engineering Research Council (NSERC) of Canada; and the Mathematics for Information Technology and Complex System (MITACS) of Canada.

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