Chapter 8
Models for HIV/AIDS

8.1 Introduction

Acquired immunodeficiency syndrome (AIDS) was first identified as a new disease in the homosexual community in San Francisco in 1981. The human immunodeficiency virus (HIV) was identified as the causative agent for AIDS in 1983. The disease has several very unusual aspects. After the initial infection, there are symptoms, including headaches and fever for 2 or 3 weeks. Transmissibility is high for about 2 months, and then there is a very long latent period during which transmissibility is low. At the end of this latent period, which may last 10 years, transmissibility rises, signaling the development of full-blown AIDS. In the absence of treatment, AIDS is invariably fatal. Now, HIV can be treated with a combination of highly active antiretroviral therapy (HAART) drugs, which both reduce the symptoms and prolong the period of low infectivity. While there is still no cure for AIDS, treatment has made it no longer a necessarily fatal disease. To describe the variation of infectivity for HIV, one possibility would be to use a staged progression model, with multiple infective stages having different infectivity. Another possibility would be to use an age of infection model.

HIV is transmitted in many ways, the most common of which are sexual contact, either heterosexual or homosexual, shared drug injection needles, and contaminated blood transfusions. Vertical transmission from mother to child is also possible. In the past, transfusions of contaminated blood were another source of disease transmission, but in developed countries screening of blood since 1985 has eliminated blood transfusions as a transmission mode.

A full model for HIV/AIDS should include a variety of transmission modes, and might take into account of many factors including the level of sexual activity, drug use, condom use, and the sexual contact network, resulting in large scale systems with many parameters that need to be estimated from data. Models were developed first for homosexual transmission. In this chapter, we will consider not only models for disease transmission in a homosexual community (the current terminology is

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men having sex with men, or MSM), but also models that include heterosexual transmission through female sex workers. We also consider modes that include the joint disease dynamics of HIV and TB and the synergy between HIV and HSV-2.

The identification of the human immunodeficiency virus [11, 55, 56, 58, 107] captured the attention of theoreticians and modelers as AIDS became one of the most feared diseases nearly three decades ago. Most of the initial modeling contributions focused on the study of the transmission dynamics of HIV at the population level since little was known about the epidemiology of HIV and, as expected, modeling was carried out first under simple settings and crude assumptions [3–7, 10, 19, 26, 32–35, 46, 48, 49, 57, 59, 65, 67–71, 75, 76, 79, 81, 88, 95–97, 102, 103]. An overview of the "state of the art" on the transmission dynamics of HIV modeling in the 1980's is found in [30], the review papers [97, 99], or in the books [8, 30, 63].

The modeling studies in [32–35, 67, 102, 103] focused on the impact that changes in the pool of susceptibles, disease-induced mortality, heterogeneous mixing, vertical transmission, asymptomatic carriers, variable infectivity, and incubation (or latent) and infective periods may have on the dynamics of sexually transmitted HIV. Efforts to model the risk of infection from sexual partner selection or from within and between group mixing became central to the research of various groups studying HIV dynamics. Other studies focused on the role of gender, core populations, and heterogenous mixing contact rates on HIV dynamics. These were naturally involved in the development of sexual-behavior surveys and data collection on sexual and "dating" activity, as well as on the mathematical modeling and analysis of heterogenous "mixing" frameworks (see [20, 21, 23, 24, 27, 28, 36–39, 41, 47, 78, 93]). The overview in [83] highlights the potential role of sexual activity and drinking on the dynamics of STDs [47, 65, 66, 93] and while the adaptive dynamics generated by changing behaviors in response, to a multitude of factors, were rarely explored, some earlier attempts were also carried out as a result of the HIV pandemic [22, 60].

As described in these historical papers [3–5], knowledge of these periods was quickly identified as critical to the initial efforts to predict the dynamics of HIV. In [35] it is observed that: "The duration of the latent period is thought to be a few days to a few weeks [3–5], and while the duration of the infectious period is not yet known, those individuals that develop full-blown AIDS have an average incubation period estimated variously at 35–47 months [88], 66 months [3], and as high as 96 months [81]." This estimate is continually being revised as information and experience accumulate. However, even the most conservative estimate suggests that it may be reasonable to approximate the infectious period by the incubation period; that is, to assume a negligible latent period. Pickering et al. [88] stress that the ability to transmit HIV is not constant, as individuals are most infectious 3–16 months following exposure, and recent studies [58, 77, 94] report the existence of two peaks of infectiousness, one taking place a few weeks after exposure and the other before the onset of "full-blown" AIDS.

In the context of the dynamics of a homosexually-active homogeneously-mixing population, the reproduction number is given by $\mathscr{R}_0 = \lambda C(T) D$, where λ denotes the probability of transmission per partner, $C(T)$ the mean number of sexual partners an average individual has per unit time when the population density is T, and D the death-adjusted mean infective period (see [35]). Since HIV is a slow disease, if $\mathscr{R}_0 \leq 1$ it will die out while if $\mathscr{R}_0 \geq 1$ it will persist in the presence of a small number of infected/infective individuals. The mathematical analysis and numerical simulations in [35] suggest that whenever the incubation period distribution is exponential the reproduction number $\mathscr{R}_0$ is a global bifurcation parameter (transcritical bifurcation), that is, as $\mathscr{R}_0$ crosses 1 a global transfer of stability from the disease-free state to the endemic equilibrium takes place, and vice versa. Local results do not depend on the distribution of times spent in the infective categories (the survivorship functions). Keeping a suite of parameters fixed [35] allowed for the comparison of the exponential incubation period distribution versus a piecewise constant survivorship (individuals remain infective for a fixed length of time). It was found that for "…some realistic parameters we can see (at least in these cases) that the reproduction numbers corresponding to these two extreme cases do not differ by more than 18% whenever the two distributions have the same mean [35]."

The inclusion of heterogeneity via the introduction of a large number of subgroups limited the forecasting capability of these models due to factors that included increased levels of uncertainty (more parameters). The use of multi-group models raised the expected modeling and parameter estimation challenges [20, 21, 23, 24, 27, 28, 36–38, 41, 65, 66, 93]. In addition, the analyses of some of these models generated novel dynamic behavior, questioning, possibly for the first time in epidemiology, the centrality of the role of the basic reproduction number in the identification and development of control, or education, or intervention measures. For example, the natural asymmetry present in disease transmission as a result of prevalent alternative modes of sexual engagement proved to be capable of giving rise to the existence of multiple equilibria [33, 34, 67]; an unexpected outcome at that time.

8.2 A Model with Exponential Waiting Times

A single homosexually-active population is divided into three classes. S denoting the number of susceptible individuals, I infective individuals, and A former I-individuals who have developed full-blown AIDS (see Fig. 8.9). We assume that all HIV-infected individuals will eventually develop full-blown AIDS (unless they die first from other causes). This, unfortunately, may be the most realistic as evidence accumulates that AIDS is a progressive disease. Later, we will suggest a project to develop a model under the assumption that some fraction of infected individuals will escape progression to full-blown AIDS. Originally, a latent class (i.e., those exposed individuals that are not yet infectious) was not included because it was believed then that the time spent in that class is short. It is further assumed that individuals who develop full-blown AIDS are no longer actively infective, that is, that they have no sexual contacts; it is also assumed that infected individuals become infective immediately. Finally, it is assumed that infective individuals acquire AIDS at the constant rate α_I per unit time and become sexually inactive at the constant rate α per unit time. Therefore, $1/(\mu + \alpha_I)$ gives the mean incubation period and $1/(\mu + \alpha)$ gives the mean sexual life expectancy.

The introduction of the model requires additional definitions. Λ will denote the constant recruitment rate into the susceptible class (individuals who are sexually active); μ the constant per-capita natural mortality rate; d the per-capita constant disease-induced mortality due to AIDS. The function $C(T)$ models the mean number of sexual partners an average individual has per unit time when the population density is T; λ (a constant) denotes the average sexual risk per infected partner; λ is often thought as the product $i\phi$ [68], where ϕ is the average number of contacts per sexual partner and i the conditional probability of infection from a sexual contact when the latter is infected. Kingsley et al. [72] had presented (not surprising) evidence that the probability of seroconversion (infection) increases with the number of infected sexual partners. Hence, $\lambda C(T)$ models the transmission rate per unit time per infected partner when the size of the sexually active population is T. Using the modeling framework published in [3, 4] with the help of Fig. 8.1, we arrive at the following epidemiological model [35] for sexually transmitted HIV under the assumption of exponential waiting times in the infection classes.

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - \lambda C(T(t))\frac{S(t)I(t)}{T(t)} - \mu S(t) \\
\frac{dI(t)}{dt} &= \lambda C(T(t))\frac{S(t)I(t)}{T(t)} - (\alpha_I + \mu)I(t) \\
\frac{dA(t)}{dt} &= \alpha_I I(t) - (\alpha + \mu)A(t)
\end{aligned} \tag{8.1}$$

where

$$T = I + S. \tag{8.2}$$

The fraction I/T can be thought of as representing the fraction of contacts that a susceptible individual has with a randomly selected infective individual. Here $\lambda C(T)SI/T$ denotes the number of newly-infected individuals per unit time since

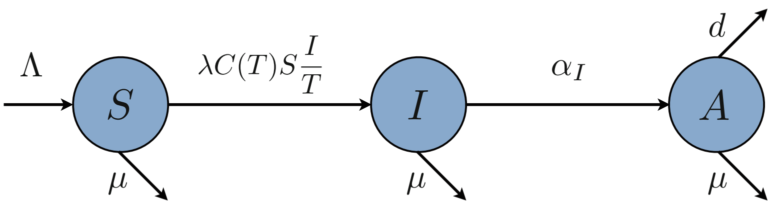

Fig. 8.1 Flow diagram: single group model in the case when all infected people will progress to AIDS

individuals in classes A are sexually inactive. A plausible assumption for modeling $C(T)$ would be to assume that it is approximately linear for small T approaching a saturation level for large values of T [62]. Here, it is assumed that $C(T)$ is a differentiable and increasing function of T (except when noted). Anderson et. al. [4] observe that $C(T)$, the mean number of sexual partners per unit time, underestimates the importance of highly active individuals and that consequently, modifications should be made to this framework in order to properly account for their role.

The analysis of the system (8.1) found in [35] makes the following assumptions concerning $C(T)$:

$$C(T) > 0, \qquad C'(T) \geq 0, \tag{8.3}$$

with prime denoting the derivative with respect to T. The dynamics of S and I are independent of A (by construction). The system is well-posed, that is, if $S(0) \geq 0$, $I(0) \geq 0$, $A(0) \geq 0$ then a unique solution exists with $S(t) \geq 0$, $I(t) \geq 0$, $A(t) \geq 0$ for $t \geq 0$.

As it is the case with most of the epidemiological systems addressed in this book, system (8.1) always has the disease-free equilibrium given by

$$(S, I, A) = \left(\frac{\Lambda}{\mu}, 0, 0\right), \tag{8.4}$$

and under certain assumptions it also supports a unique endemic equilibrium.

The stability of the disease-free equilibrium (8.4) is determined by the non-dimensional ratio

$$\mathscr{R}_0 = \lambda \left(\frac{1}{\sigma_I}\right) C \left(\frac{\Lambda}{\mu}\right), \tag{8.5}$$

that is, by the *basic reproduction number*. In the definition of $\mathscr{R}_0$, $\sigma_I = \alpha_I + \mu$, and $\mathscr{R}_0$ denotes the number of secondary infections generated by a single infective individual in a population of susceptibles at a demographic steady state. $\mathscr{R}_0$ is given by the product of the three factors (epidemiological parameters): λ (the probability of transmission per partner), $C(\Lambda/\mu)$ (the mean number of sexual partners that an average susceptible individual has per unit time when everybody in the population is susceptible), and

$$D = \left(\frac{1}{\sigma_I}\right). \tag{8.6}$$

The death-adjusted mean infective period is $D = D_I$ with D_I denoting the death-adjusted mean infectious period $1/\sigma_I$ of the I class. The use of the dimensionless ratio, $\mathscr{R}_0 = \lambda C(\Lambda/\mu) D$ leads to the following result [35]:

Theorem 8.1 *If* $\mathscr{R}_0 < 1$ *then the equilibrium* $(\Lambda/\mu, 0, 0)$ *of the system* (8.1) *is globally asymptotically stable.*

That is, every solution of (8.1) $(S(t), I(t), A(t))$ with $S(0) \geq 0$, $I(0) \geq 0$, $A(0) \geq 0$ tends to $(\Lambda/\mu, 0, 0)$ as $t \to +\infty$. That is, the condition $\mathscr{R}_0 \leq 1$ is sufficient to guarantee that the disease will eventually die out in this population.

An endemic equilibrium (S^*, I^*, A^*) of (8.1) satisfies

$$\Lambda = \left[\frac{\Lambda - \mu S^*}{\sigma_I} - \mu\right] S^*, \quad I^* = \frac{\Lambda - \mu S^*}{\alpha_I + \mu}, \quad A^* = \frac{\alpha_I}{\alpha_I + \mu} I^*.$$

In [35] it has also been established (following some of the same arguments used in other chapters) that:

Theorem 8.2 *If $\mathscr{R}_0 > 1$, there is a unique endemic equilibrium (S^*, I^*, A^*), which is locally asymptotically stable, and the disease-free state $(\Lambda/\mu, 0, 0)$ is unstable.*

We can summarize the situation (full details of all proofs are in [35]) as follows: The disease-free state of system (8.1) is globally asymptotically stable when $\mathscr{R}_0 > 1$ and unstable if $\mathscr{R}_0 > 1$. When $\mathscr{R}_0 > 1$, this system has a unique locally asymptotically stable endemic equilibrium. There is a transfer of stability to the endemic state as $\mathscr{R}_0$ crosses one. Further, when $\mathscr{R}_0 > 1$ it was shown, as one would expect, that the endemic equilibrium is also globally asymptotically stable.

The reproduction number ($\mathscr{R}_0$) increases proportionately with the transmission probability and the average number of sexual partners; it may also increase in proportion to the rate of recruitment of individuals to the susceptible class through $C(T)$. $\mathscr{R}_0$ is an increasing function of the mean infective period D and may be a decreasing function of the mortality rate (depending on the functional expression for $C(T)$).

8.3 An HIV Model with Arbitrary Incubation Period Distributions

The use of exponential waiting distributions in the I class corresponds to the requirement that the per-capita removal rate from the I class (by the development of full-blown AIDS symptoms) into the A class is constant. It would be clearly an improvement in the model of Sect. 8.2 if we were to move from constant to variable removal rates and this is what we do in this section (the ideas follow those in [19, 35]). Hence, it is still assumed that individuals become immediately infective (that is, we continue to neglect the latent period) and continue to divide the at risk population into the three classes: S, I, and A. The parameters $\lambda = i\phi$, Λ, μ, d, and p have the same meaning as in Sect. 8.2; however, the removal rates are modified through the introduction of the function $P_I(s)$ representing the proportion of individuals who become $I-$infective at time t and that, if alive, are still infective at time $t+s$ (survive as infective). The survivorship function P_I is non-negative and non-increasing, and $P_I(0) = 1$. It is further assumed that

$$\int_0^\infty P_I(s)ds < \infty,$$

and thus, $-\dot{P}_I(x)$ is the rate of removal of individuals from the class I into the class A, x time units after infection.

The number of new infections occurring at time x is $\lambda C(T(x)S(x)I(x)/T(x)$ where we have kept the meaning of $C(T)$, I, and T as in Sect. 8.2. The rate of change in the susceptible class is given now by the expression:

$$\frac{dS(t)}{dt} = \Lambda - \lambda C(T(t))S(t)\frac{I(t)}{T(t)} - \mu S(t), \tag{8.7}$$

with

$$\int_0^t \lambda C(T(x))S(x)\frac{I(x)}{T(x)}e^{-\mu(t-x)}P_I(t-x)dx$$

representing the number of individuals who have been infected from time 0 to t and are still in class I. The discount factor $\exp(-\mu(t-x))$ takes into account removals due to deaths by natural causes (not HIV). Hence, if $I_0(t)$ denotes individuals in class I at time $t = 0$ that are still infective at time t then the total number of infectives at time t is given by

$$I(t) = I_0(t) + \int_0^t \lambda C(T(x))S(x)\frac{I(x)}{T(x)}e^{-\mu(t-x)}P_I(t-x)dx, \tag{8.8}$$

where $I_0(t)$ is assumed (for biological and mathematical reasons) to have compact support (vanishing for large enough t).

The expression for $A(t)$ turns out to be the sum of three terms: $A_0e^{-(\mu+d)t}$, where $A_0 = A(0)$, representing individuals who had full-blown AIDS at time zero and are still alive; $A_0(t)$ representing individuals initially in class I who moved into class A and are still alive at time t; and those who joined the I class after time $t = 0$ (see below). We assume that $A_0(t)$ approaches zero as t approaches infinity. The term representing infected individuals "born" after time $t = 0$ is given by

$$\int_0^\tau \left\{\int_0^t \lambda C(T(x))S(x)\frac{I(x)}{T(x)}e^{-\mu(\tau-x)}[-\dot{P}_I(\tau-x)e^{-(\mu+d)(t-\tau)}]dx\right\}d\tau,$$

where $-\dot{P}_I(\tau-x)$, denotes the rate of removal from the class I at time τ or $(\tau-x)$ units after infection. Therefore

$$\begin{aligned} A(t) =& p\int_0^\tau \left\{\int_0^t \lambda C(T(x))S(x)\frac{I(x)}{T(x)}e^{-\mu(t-x)}[-\dot{P}_A(\tau-x)e^{-(t-\tau)}]dx\right\}d\tau \\ &+ A_0e^{-(\mu+d)t} + A_0(t). \end{aligned} \tag{8.9}$$

The model given by equations (8.7) is a system of nonlinear integral equations. The standard results on well-posedness for these systems, as found in [82] guarantee the existence and uniqueness of solutions and their continuous dependence on parameters. The proof of positivity is given in [32].

The basic reproduction number $\mathscr{R}_0$) of the system (8.7) is given by

$$\mathscr{R}_0 = \lambda C\left(\frac{\Lambda}{\mu}\right)\int_0^\infty P_I(x)e^{-\mu x}dx, \tag{8.10}$$

where

$$\int_0^\infty P_I(x)e^{-\mu x}dx,$$

is the death-adjusted mean infective period, D. If $P_I(x) = e^{-\alpha_I x}$ then (8.10) reduces to (8.5). We also observe that as before

$$D_I = \int_0^\infty P_I(s)e^{-\mu s}ds$$

denotes the mean infective periods of the class I.

System (8.7) with $I_0(t) = 0$ always has the equilibrium

$$(S, I) = \left(\frac{\Lambda}{\mu}, 0\right), \tag{8.11}$$

but no other constant solutions. However, since $I_0(t)$ must be zero for large t, one would expect, under appropriate assumptions, that $(\Lambda/\mu, 0)$ will be an attractor or "asymptotic equilibrium" as $t \to +\infty$. The following results have been shown in [32, 35].

Theorem 8.3 *The infection-free state* $(\Lambda/\mu, 0)$ *of the limiting system* (8.7) *is a global attractor; that is,* $\lim_{t\to+\infty}(S(t), I(t)) = (\Lambda/\mu, 0)$ *for any positive solution of system* (8.7) *as long as* $\mathscr{R}_0 \leq 1$.

Theorem 8.4 *The infection-free state of system* (8.7) *is unstable when* $\mathscr{R}_0 > 1$ *and there exists a constant* $W^* > 0$*, such that, any positive solution* $(S(t), I(t))$ *of* (8.7) *satisfies* $\limsup_{t\to+\infty} I(t) \geq W^*$.

In other words, if $\mathscr{R}_0 > 1$ the disease-free state (8.4) cannot be an attractor of any positive solution. That is, every solution has at least approximately W^* infectives (this W^* is the same as that in the statement of Theorem 8.5 below) for a sequence of times t tending to $+\infty$ and if $S(t)$, $I(t)$ approach nonzero constants as $t \to +\infty$, when $\mathscr{R}_0 > 1$ then the results in [82] guarantee that these constants must satisfy the limiting system associated with (8.7), which is given by the following set of equations:

$$\frac{dS}{dt} = \Lambda - \lambda C(T(t))S(t)\frac{I(t)}{T(t)} - \mu S(t) \tag{8.12}$$
$$I(t) = \int_0^t \lambda C(T(x))S(x)\frac{I(x)}{T(x)}e^{-\mu(t-x)}P_I(t-x)dx.$$

The limiting system (8.12) is an autonomous system for which we have established the following result:

Theorem 8.5 *If $\mathscr{R}_0 > 1$ the limiting system* (8.12) *has a unique positive equilibrium S^*, I^*. If in addition $(d/dT)(C(T)/T) \leq 0$, then this endemic equilibrium is locally asymptotic.*

Theorem 8.5 indicates that there is a switch of stability from $(\Lambda/\mu, 0)$ to (S^*, I^*) as $\mathscr{R}_0$ crosses 1. We also conjecture but have not proved that the asymptotic dynamics of system (8.7) and the limiting system (8.12) agree. An alternative approach can be found in [61]. The proofs of these results can be found in [35].

8.4 An Age of Infection Model

The model presented here is developed in [103]. We consider a homogeneously-mixing male homosexual population with infected members stratified by infection age (time since having been infected). We divide the population into three compartments: S (uninfected, but susceptible), I (HIV infected but with minimal or no symptoms), and A (fully developed AIDS). We assume members of the class A are no longer sexually active, and we let $T = S + I$ be the size of the sexually active population.

We let t denote time and τ denote age of infection, and we stratify the infected population by writing

$$I(t) = \int_0^\infty i(t,\tau)d\tau,$$

where $i(t,\tau)$ denotes the infection age density at time t. We assume:

- the mean number of sexual contacts per individual in unit time is a,
- there is a mean transmission rate $\lambda(\tau)$ at which a typical susceptible individual contracts the infection by contact with an infected individual of infection age τ,
- there is a rate $\alpha(\tau)$ of leaving the sexually active population (because of progression to AIDS) that depends on the age of infection,
- there is a constant rate of recruitment Λ into the sexually active population,

- there is a constant rate μ of departure of uninfected members from the sexually active population,
- there is a constant death rate ν from full-blown AIDS.

Under these assumptions, the fraction of members remaining in the class I τ time units after having been infected is

$$P(\tau) = e^{-\mu\tau - \int_0^\tau \alpha(\sigma)d\sigma}.$$

Then

$$i(t,\tau) = i(t-\tau, 0)P(\tau).$$

We define the total infectivity at time t,

$$W(t) = W_0(t) + \int_0^t \lambda(\tau)i(t,\tau)d\tau = W_0(t) + \int_0^t \lambda(\tau)i(t-\tau,0)P(\tau)d\tau,$$

where $W_0(t)$ is the infectivity at time t of those individuals who were infected at time $t = 0$. Then the rate of new infections in unit time is

$$B(t) = i(t,0) = a\frac{S(t)}{T(t)}W(t),$$

and

$$W(t) = W_0(t) + \int_0^t \lambda(\tau)P(\tau)B(t-\tau)d\tau.$$

We will take a to be constant, but one could assume more generally that a is a function of the total sexually active population size T.

These assumptions lead to the model

$$\begin{aligned}
S'(t) &= \Lambda - B(t) - \mu S(t) \\
W(t) &= W_0(t) + \int_0^t \lambda(\tau)P(\tau)B(t-\tau)d\tau \\
B(t) &= a\frac{S(t)}{T(t)}W(t) \\
I(t) &= I_0(t) + \int_0^t B(t-\tau)P(\tau)d\tau.
\end{aligned} \tag{8.13}$$

Since we wish to study equilibria and their stability, we consider the limit system of (8.13), namely

$$\begin{aligned} S'(t) &= \Lambda - B(t) - \mu S(t) \\ W(t) &= \int_0^\infty \lambda(\tau) P(\tau) B(t-\tau) d\tau \\ B(t) &= a \frac{S(t)}{T(t)} W(t) \\ I(t) &= \int_0^\infty B(t-\tau) P(\tau) d\tau. \end{aligned} \tag{8.14}$$

In order to obtain an expression for the number of active AIDS cases, not part of the model since individuals in the class A are assumed not to have any further sexual contacts, but included because it provides a relation that may be compared with data, we differentiate the equation

$$I(t) = \int_0^t B(s) P(t-s) ds$$

of (8.14), using

$$P'(u) = -[\mu + \alpha(u)] P(u).$$

We obtain

$$I'(t) = B(t) - \mu I(t) - \int_0^t B(s) \alpha(t-s) P(t-s) ds.$$

The input to the AIDS class A is

$$\int_0^t B(s) \alpha(t-s) P(t-s) ds.$$

Thus the number of active AIDS cases is given by

$$A'(t) = \int_0^\infty \alpha(t-s) P(t-s) B(s) ds - \nu A(t).$$

Analysis of the model (8.14) would be considerably simpler if we had assumed mass action incidence rather than standard incidence, because use of standard incidence brings $T(t) = S(t) + I(t)$ into the model. However, mass action incidence is much less plausible for sexual transmission models than standard incidence. For the model it is not difficult to show that the basic reproduction number is given by

$$\mathscr{R}_0 = a \int_0^\infty \lambda(\tau) P(\tau) d\tau,$$

and that there is a disease-free equilibrium $S = \Lambda/\mu, I + B = W = 0$ which is asymptotically stable if $\mathscr{R}_0 < 1$. Calculation of the endemic equilibrium is more difficult, but it is possible to show that there is an endemic equilibrium that is asymptotically stable at least for values of $\mathscr{R}_0$ larger than 1 but close to 1. For larger values of $\mathscr{R}_0$ the endemic equilibrium may be unstable, and there may be a Hopf bifurcation [64] and sustained oscillatory solutions of the model.

8.5 *HIV and Tuberculosis: Dynamics of Coinfections

HIV diminishes the ability of the immune system to respond to invasions by infectious agents such as *M. tuberculosis*. Furthermore, as HIV infection progresses, immunity often declines with patients becoming more susceptible to typical or rare infections. In wealthier societies HIV and TB treatments are common; these drugs have altered significantly the joint dynamics of TB and HIV.

The modeling literature on the independent dynamics of HIV or TB is quite extensive. TB efforts include, for example, [9, 18, 40, 42, 43, 50, 51, 89] while HIV/AIDS include [31, 63, 80, 103] to name a few more. TB/HIV coinfection modeling efforts have also been published. Kirschner [73] developed an immunological model describing HIV-1 and TB coinfections within a host. Naresh et al. [86] introduced a model involving a population sub-divided into four epidemiological classes: susceptible, TB infective, HIV infective, and those with AIDS; a model focusing on the transmission dynamics of HIV and treatable TB in variable size populations. Schulzer et al. [101] looked at HIV/TB joint dynamics using actuarial methods. West and Thompson [105] introduced models for the joint dynamics of HIV and TB that were explored via numerical simulations; their main goal was to estimate parameters and use their estimates to forecast the future transmission of TB in the United States. Porco et al. [90] looked, using a discrete event simulation model, at the impact of HIV on the probability and expected severity of TB outbreaks. Additional efforts include those in [91, 98].

A system of differential equations is used in [92] to model the joint dynamics of TB and HIV. The total population is divided into the following epidemiological subgroups: S, susceptible; L, latent with TB; I, infectious with TB; T, successfully treated with TB; J_1, HIV infectious; J_2, HIV infectious and TB latent; J_3, infectious with both TB and HIV; and A, "full-blown" AIDS. The compartmental diagram in Fig. 8.2 illustrates the flow of individuals as they face the possibility of acquiring specific-disease infections or even coinfections.

The TB/HIV model is given by the following systems of eight ordinary differential equations:

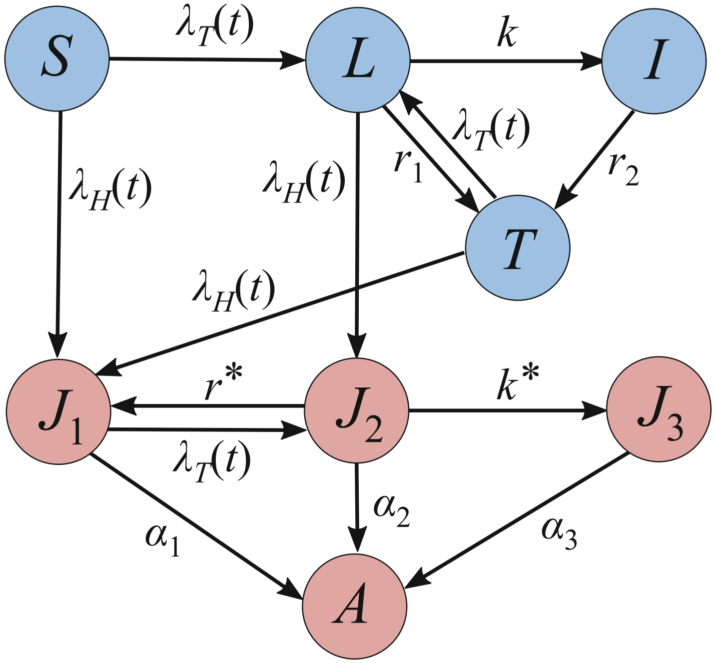

Fig. 8.2 Transition diagram between classes for the dynamics of TB and HIV coinfections. The force of infection for TB is $\lambda_T = c(I + J_3)/N$, and the force of infection for HIV is $\lambda_H = \sigma J^*/R$, where $J^* = J_1 + J_2 + J_3$

$$
\textbf{TB}: \quad
\begin{aligned}
\frac{dS}{dt} &= \Lambda - cS\frac{I + J_3}{N} - \sigma S\frac{J^*}{R} - \mu S \\
\frac{dL}{dt} &= c(S + T)\frac{I + J_3}{N} - \sigma L\frac{J^*}{R} - (\mu + k + r_1)L \\
\frac{dI}{dt} &= kL - (\mu + d + r_2)I \\
\frac{dT}{dt} &= r_1 L + r_2 I - cT\frac{I + J_3}{N} - \sigma T\frac{J^*}{R} - \mu T,
\end{aligned}
\tag{8.15a}
$$

$$
\textbf{HIV}: \quad
\begin{aligned}
\frac{dJ_1}{dt} &= \sigma(S + T)\frac{J^*}{R} - cJ_1\frac{I + J_3}{N} - (\alpha_1 + \mu)J_1 + r^* J_2 \\
\frac{dJ_2}{dt} &= \sigma L\frac{J^*}{R} + cJ_1\frac{I + J_3}{N} - (\alpha_2 + \mu + k^* + r^*)J_2 \\
\frac{dJ_3}{dt} &= k^* J_2 - (\alpha_3 + \mu + d^*)J_3 \\
\frac{dA}{dt} &= \alpha_1 J_1 + \alpha_2 J_2 + \alpha_3 J_3 - (\mu + f)A,
\end{aligned}
\tag{8.15b}
$$

Table 8.1 Definition of parameters and state variables used in the TB/HIV model (8.15)

Symbol	Definition
N	Total population
R	Total active population ($= N - I - J_3 - A = S + L + T + J_1 + J_2$)
J^*	Individuals with HIV who have not developed AIDS ($= J_1 + J_2 + J_3$)
Λ	Constant recruitment rate
c	Transmission rate of TB
σ	Transmission rate of HIV
μ	Per-capita natural death rate
k	Per-capita TB progression rate for individuals not infected with HIV
k^*	Per-capita TB progression rate for individuals infected also with HIV
d	Per-capita TB-induced death rate
d^*	Per-capita HIV-induced death rate
f	Per-capita AIDS-induced death rate
r_1	Per-capita latent TB treatment rate for individuals with no HIV
r_2	Per-capita active TB treatment rate for individuals with no HIV
r^*	Per-capita latent TB treatment rate for individuals with also HIV
α_i	Per-capita AIDS progression rate for individuals in the J_i ($i = 1, 2, 3$)

where

$$\begin{aligned} N &= S + L + I + T + J_1 + J_2 + J_3 + A, \\ R &= N - I - J_3 - A = S + L + T + J_1 + J_2, \\ J^* &= J_1 + J_2 + J_3. \end{aligned} \tag{8.16}$$

The variable R here collects non-infectious "circulating" individuals, that is, those who do not have active TB or AIDS. Definitions of model parameters are collected in Table 8.1.

The modeling assumptions include: homogenous mixing; HIV positive and TB infective (J_3) showing severe HIV symptoms cannot be effectively treated for active TB; TB infections are only acquired through contacts with TB infectious individuals (I and J_3); and individuals may acquire HIV infections only through contacts with HIV infectious individuals (J^* group). Further, the "probability" of infection per contact is assumed to be the same for T and S classes (β and λ). Furthermore, I (TB infectious), J_3 (TB and HIV infectious), and A (AIDS) individuals are too ill to remain sexually active and, consequently, they do not transmit HIV through sexual activity. Hence, $R \equiv N - I - J_3 - A$ and the HIV incidence is modeled by $\sigma J^*/R$ (see [29, 74, 108]).

The probability of having a contact with HIV infectious individuals is modeled as J^*/R and the number of new HIV infections in a unit time is therefore $\sigma S J^*/R$ [IV drug injections, vertically-transmitted HIV (children of birth), or HIV transmission via breast feeding, forms of HIV transmission are ignored]. The most drastic in this model comes from the incorporation of sexual transmission as an indirect risk factor, a function of HIV prevalence. Further, demographic changes are ignored or alternatively, it is assumed that the time scale under consideration is such that changes in population size are not too significant.

The TB control reproduction number (under treatment) is given by the expression

$$\mathscr{R}_1 = \frac{ck}{(\mu + k + r_1)(\mu + d + r_2)} \tag{8.17}$$

while the HIV reproduction number is

$$\mathscr{R}_2 = \frac{\sigma}{\alpha_1 + \mu}. \tag{8.18}$$

$\mathscr{R}_1$ is the product of the average number of susceptible infected by one TB infective individual over its effective infective period, $c/(\mu+d+r_2)$, and the fraction of the population that survives the TB latent period, $k/(\mu + k + r_1)$. $\mathscr{R}_1$ denotes the number of secondary TB infectious cases generated by a typical TB infective individual during its effective infective period if introduced in a population of mostly TB-susceptible individuals, in a population where TB treatment is accessible. $\mathscr{R}_2$ is the HIV reproduction number in a TB-free society, the number of secondary HIV infections produced by an HIV infectious (but not TB-infected) individual during its infectious period if introduced in a population of HIV-susceptible individuals (in a TB-free world). The reproduction numbers do not involve the parameters tied in to the dynamics of TB-HIV coinfection, that is, k^* and α_3.

Consequently, the reproduction number for system (8.15) under TB treatment is given by

$$\mathscr{R} = \max\{\mathscr{R}_1, \mathscr{R}_2\}.$$

We have shown in [92] that TB and HIV will die out if $\mathscr{R} < 1$ while either or both diseases may become endemic if $\mathscr{R} > 1$.

In [92], it was shown that system (8.15) is well-posed, that is, solutions that start in this octant where all the variables are non-negative stay there. It was also shown that system (8.15) has three possible non-negative boundary equilibria: the disease-free equilibrium (DFE) or E_0, the TB-only (HIV-free) equilibrium or E_T, and the HIV-only (TB-free) equilibrium or E_H. The components of E_0 are

$$S_0 = \frac{\Lambda}{\mu},\ L_0 = I_0 = T_0 = J_{01} = J_{02} = J_{03} = A_0 = 0.$$

The E_T components are

$$S_T = \frac{\Lambda}{\mu + cI_T/N_T}, \quad L_T = \frac{I_T}{R_{1b}}, \quad I_T = \frac{N_T(\mathscr{R}_1 - 1)}{\mathscr{R}_1 + \mathscr{R}_{1a}}, \quad T_T = \frac{(r_1 L + r_2 I_T)S_T}{\Lambda},$$
$$J_{1T} = J_{2T} = J_{3T} = A_T = 0,$$

where

$$N_T = \frac{\Lambda}{\mu + d(\mathscr{R}_1 - 1)/(\mathscr{R}_1 + \mathscr{R}_{1a})},$$

with

$$\mathscr{R}_{1a} = \frac{c}{\mu + k + r_1}, \; \mathscr{R}_{1b} = \frac{k}{\mu + d + r_2}. \tag{8.19}$$

The E_H components are

$$S_H = \frac{\Lambda}{\mu \mathscr{R}_2 + \alpha_1(\mathscr{R}_2 - 1)}, \quad L_H = I_H = T_H = 0,$$
$$J_{1H} = (\mathscr{R}_2 - 1)S_H, \quad J_{2H} = J_{3H} = 0, \quad A_H = \frac{\alpha_1 J_{1H}}{\mu + f}.$$

The following results were established in [92]:

Theorem 8.6 *The disease-free equilibrium E_0 is locally asymptotically stable if $\mathscr{R} < 1$, and it is unstable if $\mathscr{R} > 1$.*

Theorem 8.7 *The HIV-free equilibrium E_T is locally asymptotically stable if $\mathscr{R}_1 > 1$ and $\mathscr{R}_2 < 1$.*

We observe that E_H may not be locally asymptotically stable under the conditions $\mathscr{R}_1 < 1$ and $\mathscr{R}_2 > 1$. Our numerical studies show that when $\mathscr{R}_1 < 1$ and $\mathscr{R}_2 > 1$ it is possible that the equilibrium E_H is unstable and TB can coexist with HIV [92]. Further, whenever both reproduction numbers are greater than 1, that is, $\mathscr{R}_1 > 1$ and $\mathscr{R}_2 > 1$, E_T and E_H both exist and E_0 is unstable. Our numerical studies show that all three boundary equilibria are unstable and solutions converge to an interior equilibrium point. Furthermore, partial analytical results and numerical simulations support the existence of an interior equilibrium $\hat{E}$ when both reproduction numbers, $\mathscr{R}_1$ and $\mathscr{R}_2$, are greater than 1. The numerical simulations of the system further suggest that the interior equilibrium is LAS in most cases although the possibility of stable periodic solutions seems likely [92].

When both reproduction numbers are greater than 1, i.e., $\mathscr{R}_1 > 1$ and $\mathscr{R}_2 > 1$, E_T and E_H both exist and E_0 is unstable. In this case, the numerical simulations of the model show that it is possible that all three boundary equilibria are unstable and solutions converge to an interior equilibrium point. Although explicit expressions for an interior equilibrium are very difficult to compute analytically, we have managed to obtain some relationships that can be used to determine the existence of an interior equilibrium.

Let $\hat{E} = (\hat{S}, \hat{L}, \hat{I}, \hat{J}_1, \hat{J}_2, \hat{J}_3, \hat{A})$ denote an interior equilibrium with all components positive, and let x and y denote the fractions:

$$x = \frac{\hat{I} + \hat{J}_3}{\hat{N}} > 0 \quad \text{and} \quad y = \frac{\hat{J}^*}{\hat{R}} > 0. \tag{8.20}$$

Note that x and y correspond to the levels of disease prevalence for TB and HIV, respectively.

By setting the right-hand-side of the system (8.15) equal to zero we can obtain the following two equations for x and y:

$$\begin{aligned} x &= xF(x, y), \\ y &= yG(x, y), \end{aligned} \tag{8.21}$$

where

$$\begin{aligned} F(x, y) &= \frac{c}{\hat{N}}\Big[\frac{k\hat{S}}{(\mu + d + r_2)B_1} + \frac{k^*}{\Delta_2\Delta_3}\Big(\frac{\hat{S}\sigma y}{B_1} + \hat{J}_1\Big)\Big], \\ G(x, y) &= \frac{\sigma}{\hat{R}}\Big\{\frac{1}{B_2}\Big(\hat{S} + \hat{T} + \frac{r^*\hat{L}}{\Delta_2}\Big)\Big(1 + \frac{cx}{\Delta_2}\Big[1 + \frac{k^*}{\Delta_3}\Big]\Big) + \frac{\hat{L}}{\Delta_2}\Big[1 + \frac{k^*}{\Delta_3}\Big]\Big\}, \end{aligned} \tag{8.22}$$

in which

$$\begin{aligned} &\hat{S} = \frac{\Lambda}{\mu + cx + \sigma y}, \quad \hat{L} = \frac{c\Lambda}{B_1(\mu + cx + \sigma y)}x, \quad \hat{I} = \frac{k}{\mu + d + r_2}\hat{L}, \\ &\hat{T} = \frac{r_1 + \frac{r_2 k}{\mu + d + r_2}}{cx + \sigma y + \mu}\hat{L}, \quad \hat{J}_1 = \frac{\big(\hat{S} + \hat{T} + \frac{r^*\hat{L}}{\Delta_2}\big)\sigma y}{B_2}, \quad \hat{J}_2 = \frac{\hat{L}\sigma y + \hat{J}_1 cx}{\Delta_2}, \\ &\hat{J}_3 = \frac{k^*(\hat{L}\sigma y + \hat{J}_1 cx)}{\Delta_2\Delta_3}, \quad \hat{A} = \frac{1}{\mu + f}\big(\alpha_1\hat{J}_1 + \alpha_2\hat{J}_2 + \alpha_3\hat{J}_3\big), \end{aligned} \tag{8.23}$$

and

$$\begin{aligned} \Delta_2 &= \alpha_2 + \mu + k^* + r^*, \\ \Delta_3 &= \alpha_3 + \mu + d, \\ B_1 &= \sigma y + \mu + k + r_1 - \frac{cx(r_1 + \frac{r_2 k}{\mu + d + r_2})}{cx + \sigma y + \mu} \\ &\geq \sigma y + \mu + k + r_1 - (r_1 + k) \\ &> 0, \\ B_2 &= \frac{cx(\alpha_1 + \mu + k^*)}{\Delta_2} + \alpha_1 + \mu. \end{aligned} \tag{8.24}$$

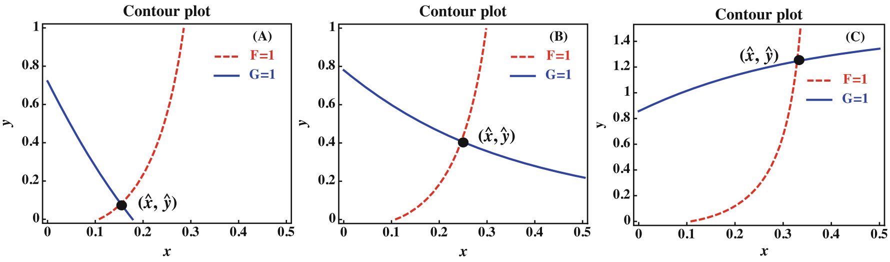

Fig. 8.3 Contour plots showing the intersection points of the curves $F(x, y) = 1$ (dashed curve) and $G(x, y) = 1$ (solid curve) for various values of $\mathscr{R}_2$ with $\mathscr{R}_1$ being fixed at 1.5 ($c = 12$). The values of $\mathscr{R}_2$ in (**A**)–(**C**) are 3.6, 4.6, and 7, respectively (corresponding to $\lambda\sigma = 0.41, 0.52,$ and 0.8). The axes are $x = (I + J_3)/N$ and $y = J^*/R$, representing the factors in the incidence functions for TB and HIV, respectively. The intersection $(\hat{x}, \hat{y}) = (\frac{\hat{I}+\hat{J}_3}{\hat{N}}, \frac{\hat{J}^*}{\hat{R}})$ determines components of the interior equilibrium $\hat{E}$ if $0 < \hat{x} < 1$ and $\hat{y} > 0$

Note that $x > 0$ and $y > 0$, Eq. (8.21) reduces to

$$F(x, y) = 1, \quad G(x, y) = 1, \tag{8.25}$$

and an intersection of the two curves determined by Eq. (8.25), denoted by $\hat{x}$ and $\hat{y}$, corresponds to a coexistence equilibrium of TB and HIV. We can consider $\hat{x}$ as a measure for the TB prevalence. The intersection property of the two curves given by $F(x, y) = 1$ and $G(x, y) = 1$ are illustrated in Fig. 8.3.

Figure 8.3 plots the intersection point $(\hat{x}, \hat{y})$ of the contour plots of $F(x, y) = 1$ (dashed curve) and $G(x, y) = 1$ (solid curve) for several values of $\mathscr{R}_2$ with $\mathscr{R}_1$ being fixed ($\mathscr{R}_1 = 1.5$ corresponding to $c = 12$). Again, an interior equilibrium $\hat{E}$ can be determined by $\hat{x}$ and $\hat{y}$ if $0 < \hat{x} < 1$ and $\hat{y} > 0$. This figure illustrates how $\hat{x}$ changes with increasing $\mathscr{R}_2$. We have chosen $k^* = 5k$ (i.e., the progression rate to active TB in individuals with both latent TB and HIV is five times higher than that in individuals with latent TB only), $\alpha_3 = 5\alpha_1$ (i.e., the progression to AIDS in individuals with active TB is five times higher than that in individuals without TB). For this set of parameter values, the values of $\mathscr{R}_2$ in Fig. 8.3A–C are 3.6, 4.6, and 7, respectively. It shows that when $\mathscr{R}_2$ increases from 3.8 to 4.6, the $F(x, y) = 1$ curve does not change much while the right-end of the $G(x, y) = 1$ curve moves to the right of the $F = 1$ curve. This leads to an intersection point of the two curves (see (A) and (B)), which corresponds to an interior equilibrium $\hat{E}$. When $\mathscr{R}_2$ is further increased to 7, the $G(x, y) = 1$ curve changes from decreasing to increasing (see (C)). Although there is still a unique intersection point, the $y = \hat{J}^*/\hat{R}$ component may become greater than 1. This is still biologically feasible as J/R can exceed 1 (see (C)). The intersection points in (A)-(C) are $(\hat{x}, \hat{y}) = (\frac{\hat{I}+\hat{J}_3}{\hat{N}}, \frac{\hat{J}^*}{\hat{R}}) = (0.15, 0.07), (0.25, 0.4), (0.33, 1.25)$, respectively. We observe that $\hat{x}$ increases with $\mathscr{R}_2$ from 0.15 to 0.33. This implies that the prevalence of HIV may have significant impact on the infection level of TB.

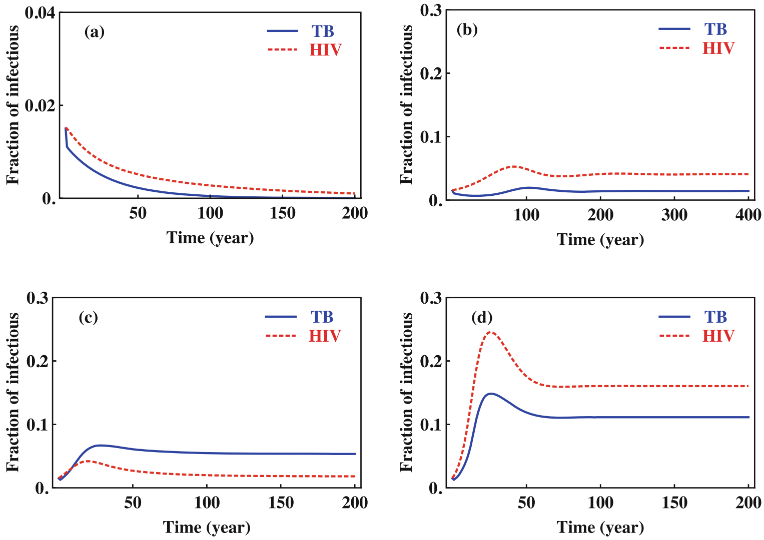

Fig. 8.4 Time plots of prevalence of TB and HIV. The TB curves (solid) represent the fraction of active TB ($(I + J_3)/N$), and the HIV curve (dashed) represents the activity-adjusted fraction of HIV (J^*/R)

Figure 8.4 examines changes in infection levels over time. It plots the time series of $[I(t) + J_3(t)]/N(t)$ (fraction of active TB) and $J^*(t)/R(t)$ (activity-adjusted fraction of HIV infectious) for fixed $\mathscr{R}_1$ and various $\mathscr{R}_2$. The top two figures are for the case when the reproduction number for TB is less than 1 ($\mathscr{R}_1 = 0.96 < 1$ or $c = 7.5$), and the reproduction number for HIV is $\mathscr{R}_2 = 0.9 < 1$ (or $\sigma = 0.105$) in (a) and $\mathscr{R}_2 = 1.3 > 1$ (or $\sigma = 0.15$) in (a). It illustrates in Fig. 8.4a that TB cannot persist if $\mathscr{R}_2 < 1$. However, if $\mathscr{R}_2 > 1$ then it is possible that TB can become prevalent even if $\mathscr{R}_1 < 1$ (see Fig. 8.4b). The bottom two figures are for the case when the reproduction number of TB is greater than 1 ($\mathscr{R}_1 = 1.2$, or $c = 9.1$), and $\mathscr{R}_2 = 2$ (or $\sigma = 0.23$) in (c) and $\mathscr{R}_2 = 3$ (or $\sigma = 0.34$) in (d). It demonstrates that an increase in $\mathscr{R}_2$ will lead to an increase in the level of TB prevalence as well. All other parameters are the same as in Fig. 8.3 except that $k^* = 3k$.

Another way to look at the role of HIV on TB dynamics is to compare the outcomes between the cases where HIV is absent or present (instead of varying the value of $\mathscr{R}_2$). This result is presented in Fig. 8.5. The reproduction numbers are identical in Fig. 8.5A, B: $\mathscr{R}_1 = 0.98 < 1$ ($c = 7.7$) and $\mathscr{R}_2 = 1.2 > 1$ ($\sigma = 0.137$). Other parameter values are the same as in Fig. 8.4 except that $k^* = k$. The variables plotted are $(I + J_2)/N$ and J^*/N. Figure 8.5A is for the case when HIV is absent by letting $J^*(0) = 0$. It shows that TB cannot persist. In Fig. 8.5B, the initial value of HIV is positive (i.e., $J^*(0) > 0$). It shows that both TB and HIV coexist.

Examples of other mathematical models on dynamics of TB/HIV coinfections include [73, 86, 90, 91, 101].

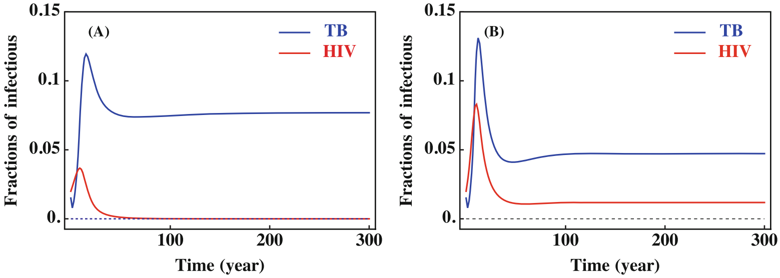

Fig. 8.5 For the plot in (**A**), HIV is absent by letting $J^*(0) = 0$. It shows that TB cannot persist. In (**B**), the initial value of HIV is positive (i.e., $J^*(0) > 0$). It shows that both TB and HIV will coexist

8.6 *Modeling the Synergy Between HIV and HSV-2

The example presented in this section considers the synergy between HIV and HSV-2. One of the questions that is of interest for public health officials is how treatment of HSV-2 may influence the prevalence and control of HIV.

Several mathematical models have been developed to investigate the transmission dynamics of HSV-2 (e.g., [17, 53, 87, 100] and references therein) and HIV (e.g., [12–14, 44, 84, 85] and references therein). To our knowledge, however, there have only been a few modeling studies of the epidemiological synergy between HSV-2 and HIV. Using the individual-based model STDSIM, White et al. [106] studied the population-level effect of HSV-2 therapy on the incidence of HIV in sub-Saharan Africa. Foss et al. [54] developed a dynamic HSV/HIV model to estimate the contribution of HSV-2 to HIV transmission from clients to female sex workers in southern India and the maximum potential impact of "perfect" HSV-2 suppressive therapy on HIV incidence. Blower and Ma [16] used a transmission model that specifies the dynamics of HIV and HSV-2 to predict the effect of a high-prevalence HSV-2 epidemic on HIV incidence. Abu-Raddad et al. [1] constructed a deterministic compartmental model to describe HIV and HSV-2 transmission dynamics and their interaction. However, the model studied in [16] does not include heterogeneity in sexual activity and assumes that individuals mix randomly, whereupon each infective individual is equally likely to spread the disease to all others. Also, gender is not incorporated into the models studied by either [16] or [1]. The models in [54, 106] incorporate various heterogeneities, including gender and/or age, but not sexual activity, and only numerical simulations are conducted.

Gender may be an important factor in modeling the epidemiological synergy between HSV-2 and HIV as shown in the meta-analysis of several studies that male parameters differ from the corresponding female parameters. For example, the male-to-female HSV-2 transmission probability is greater than the female-to-male transmission probability [45, 104], and thus the risk of female-to-male transmission per sex act is less than the risk of male-to-female transmission [84, 85]. Thus, to fully understand the epidemiological synergy between HSV-2 and HIV and to investigate measures for controlling these sexually transmitted diseases, it is important to analyze models that consider heterogeneities in sexual activity, mixing within and between different activity groups and genders.

In [2, 52], a model incorporating both HIV and HSV-2 infections was analyzed. The model considers one male population and multiple female populations based on their activity levels with variable male preferences to different female groups. Results from the model demonstrate that the heterogeneity in activity levels and male preference in mixing may play an important role in model outcomes. More details of the model analysis are presented below.

Consider a population consisting of sexually active female and male individuals. Consider the case in which the female population is divided into subgroups based on levels of sexual activity (e.g., number of partners) with a low-risk group (e.g., members of the general population) and a high-risk group (e.g., sex workers), while all individuals in the male population have the same activity level. These subpopulations are labeled by the subscripts f_1, f_2, m, which denote low- and high-risk females and males, respectively. Let N_i denote the population sizes of groups i, where $i = m, f_1, f_2$. The population in each group is assumed to be homogeneous in the sense that individuals have the same infectious period, duration of immunity, contact rate, and so on. We divide the progression of HIV into two stages, acute infection and AIDS. Similarly, HSV-2 is represented by acute and latent infection stages. Because individuals infected with HIV alone or HSV-2 alone can become coinfected with both HIV and HSV-2, each group i ($i = m, f_1, f_2$) is further divided into seven epidemiological classes or subgroups: susceptible, infected with acute HSV-2 only (A_i), infected with latent HSV-2 only (L_i), infected with HIV only (H_i), infected with HIV and acute HSV-2 (P_i), infected with HIV and latent HSV-2 (Q_i) and AIDS (D_i). A transition diagram between these epidemiological classes within group i is depicted in Fig. 8.6.

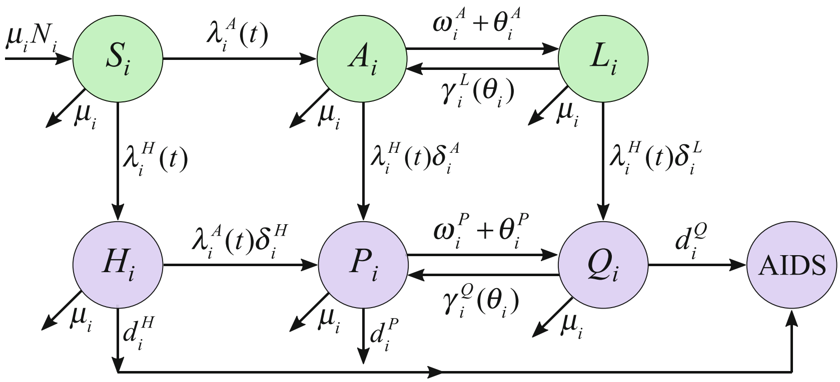

Fig. 8.6 Transition diagram of the coupled dynamics between HIV and HSV-2. The top row includes classes infected with HSV-2 only, and the bottom row includes classes infected with either HIV only or coinfected with HIV and HSV-2

For each sub-population i ($i = f_1, f_2, m$) there is a per-capita recruitment rate μ_i into the susceptible group. For all classes there is a constant per-capita rate μ_i of exiting the sexually active population. Thus, the total population N_i in group i remains constant for all time. Susceptible people in group i acquire infection with HSV-2 or HIV at the rate $\lambda_i^A(t)$ or $\lambda_i^H(t)$, respectively. Upon being infected with HSV-2, people in group i enter the class A_i (infected with acute HSV-2 only). These individuals become latent L_i at the constant rate ω_i^A (an average duration in A_i is $1/\omega_i^A$). Following an appropriate stimulus in individuals with latent HSV-2, reactivation may occur [17]. We assume that people with latent HSV-2 only reactivate at the rate γ_i^L. Individuals with HIV are assumed to develop AIDS at the rate d_i^H. Let δ_i^A and δ_i^L denote the enhanced susceptibility to HIV infection for individuals in group i with acute or latent HSV-2 infection. Classes P_i and Q_i are similar to A_i and L_i, respectively, except that A_i and L_i denote individuals with HSV-2 only whereas P_i and Q_i denote individuals with coinfections. The difference in stage durations is indicated by the superscripts (e.g., $1/\gamma_i^L$ for the L class and $1/\gamma_i^Q$ for the Q class). Finally, the antiviral treatment rates for the A_i and P_i individuals are denoted by θ_i^A and θ_i^Q, respectively. Because antiviral medications will also suppress reactivation of latent HSV-2, we assume that the reactivation rate of people with latent HSV-2 γ_i^L (or γ_i^Q) is a decreasing function of θ_i^A (or θ_i^P), denoted by $\gamma_i^L(\theta_i^A)$ (or $\gamma_i^Q(\theta_i^P)$). The sources for most of the parameter values are from [1, 53] (see [52] for more details).

Based on Fig. 8.6, Alvey et al. [2] studied the following model:

$$
\begin{aligned}
\frac{dS_i}{dt} &= \mu_i N_i - (\lambda_i^A(t) + \lambda_i^H(t))S_i - \mu_i S_i,\\
\frac{dA_i}{dt} &= \lambda_i^A(t)S_i + \gamma_i^L(\theta_i^A)L_i - \delta_i^A\lambda_i^H(t)A_i - (\omega_i^A + \theta_i^A + \mu_i)A_i,\\
\frac{dL_i}{dt} &= (\omega_i^A + \theta_i^A)A_i - \delta_i^L\lambda_i^H(t)L_i - (\gamma_i^L(\theta_i^A) + \mu_i)L_i,\\
\frac{dH_i}{dt} &= \lambda_i^H(t)S_i - \delta_i^H\lambda_i^A(t)H_i - (\mu_i + d_i^H)H_i,\\
\frac{dP_i}{dt} &= \delta_i^A\lambda_i^H(t)A_i + \delta_i^H\lambda_i^A(t)H_i + \gamma_i^Q(\theta_i^P)Q_i - (\omega_i^P + \theta_i^P + \mu_i + d_i^P)P_i,\\
\frac{dQ_i}{dt} &= \delta_i^L\lambda_i^H(t)L_i + (\omega_i^P + \theta_i^P)P_i - (\gamma_i^Q(\theta_i^P) + \mu_i + d_i^Q)Q_i, \quad i = m, f_1, f_2,
\end{aligned}
\tag{8.26}
$$

where the functions $\lambda_i^j(t)$ represent the forces of infection given below. Let b_i ($i = m, f_1, f_2$) be the rate at which individuals in group i acquire new sexual partners (also referred to as contact rates), and let c_j denote the probability that a male chooses a female partner in group j ($j = f_1, f_2$). Then $c_1 + c_2 = 1$. For ease of notation, let

$$c_1 = c, \quad c_2 = 1 - c.$$

Overall, the number of female partners in groups j ($j = f_1, f_2$) that males acquire should be equal to the number of male partners that females in groups j acquire. These observations lead to the following balance conditions:

$$b_m c N_m = b_{f_1} N_{f_1}, \qquad b_m(1-c)N_m = b_{f_2} N_{f_2}. \tag{8.27}$$

To ensure that constraints in (8.27) are satisfied, we assume in numerical simulations that b_m and c are fixed constants with b_{f_1} and b_{f_2} being varied according to N_m, N_{f_1}, and N_{f_2}.

The force of infection functions can be expressed as

$$\begin{aligned}
\lambda_m^H(t) &= \sum_{i=1}^{2} b_m c_i \beta_{f_i m}^H \frac{H_{f_i} + \delta_{f_i}^P P_{f_i} + \delta_{f_i}^Q Q_{f_i}}{N_{f_i}}, \\
\lambda_{f_j}^H(t) &= b_{f_j} \beta_{m f_j}^H \frac{H_m + \delta_m^P P_m + \delta_m^Q Q_m}{N_m}, \quad j = 1, 2, \\
\lambda_m^A(t) &= \sum_{i=1}^{2} b_m c_i \beta_{f_i m}^A \frac{A_{f_i} + \sigma_{f_i}^P P_{f_i}}{N_{f_i}}, \\
\lambda_{f_j}^A(t) &= b_{f_j} \beta_{m f_j}^A \frac{A_m + \sigma_m^P P_m}{N_m}, \quad j = 1, 2,
\end{aligned} \tag{8.28}$$

where

$$N_i = S_i + A_i + L_i + H_i + P_i + Q_i, \quad i = m, f_1, f_2$$

denotes the total population size of group i. In (8.28), β_{im}^H (β_{mi}^H), $i = f_1, f_2$ are the HIV transmission probabilities per partner between females infected with HIV in group i and susceptible males (between males infected with HIV and susceptible females in group i); β_{im}^A (β_{mi}^A), $i = f_1, f_2$ are the HSV-2 transmission probabilities per partner between females infected with acute HSV-2 in group i and susceptible males (between males infected with acute HSV-2 and susceptible females in group i); δ_i^P and δ_i^Q ($i = m, f_1, f_2$) are the enhanced HIV infectiousness of coinfected individuals, and σ_i^P ($i = m, f_1, f_2$) are the enhanced HSV-2 infectiousness of coinfected individuals.

8.6.1 Reproduction Numbers for Individual Diseases

For each of the two diseases, we can compute the reproduction number in the absence of the other disease. Let $\mathscr{R}_0^A$ and $\mathscr{R}_0^H$ denote these reproduction numbers for HSV-2 and HIV, respectively. Due to the loop between the symptomatic and asymptomatic stages of HSV-2, the derivation of analytical expression for $\mathscr{R}_0^A$ for model (8.26) is not straightforward. A detailed derivation of the following formula for $\mathscr{R}_0^A$ can be found in [2, 52]:

$$\mathscr{R}_0^A = \sqrt{\left(\mathscr{R}_{mf_1m}^A\right)^2 + \left(\mathscr{R}_{mf_2m}^A\right)^2}, \tag{8.29}$$

where

$$\mathscr{R}_{mf_jm}^A = \sqrt{\frac{b_{f_j}\beta_{mf_j}^A}{\omega_m^A + \theta_m^A + \mu_m} \cdot P_m^A \cdot \frac{b_m c_j \beta_{f_jm}^A}{\omega_{f_j}^A + \theta_{f_j}^A + \mu_{f_j}} \cdot P_{f_j}^A}, \quad j = 1, 2$$

with P_i^A $(i = m, f_1, f_2)$ representing the probability that an individual of group i is in the acute stage (A), which is given by

$$P_i^A = \frac{\left(\omega_i^A + \theta_i^A + \mu_i\right)\left(\gamma_i^L(\theta_i^A) + \mu_i\right)}{\left[\gamma_i^L(\theta_i^A) + \omega_i^A + \theta_i^A + \mu_i\right]\mu_i}, \quad i = m, f_1, f_2. \tag{8.30}$$

The formulas for P_i^A in (8.30) can be explained as follows. Let

$$p = \frac{\omega_i^A + \theta_i^A}{\omega_i^A + \theta_i^A + \mu_i}, \quad q = \frac{\gamma_i^L}{\gamma_i^L + \mu_i},$$

where p represents the probability that an individual moves from the acute stage (A) to the latent stage (L), and q represents the probability that an individual moves from L to A. Thus, the probability that an individual is in the acute stage within the $A \rightleftharpoons L$ loop is

$$\sum_{k=1}^{\infty}(pq)^k = \frac{\left(\omega_i^A + \theta_i^A + \mu_i\right)\left(\gamma_i^L + \mu_i\right)}{\left(\gamma_i^L + \omega_i^A + \theta_i^A + \mu_i\right)\mu_i} = P_i^A.$$

Notice that in the formula for $\mathscr{R}_0^A$ the balance conditions in (8.27) have been used. Other factors in $\mathscr{R}_{mf_im}^A$ $(i = 1, 2)$ also have clear biological interpretations:

- $b_{f_j}\beta_{mf_j}^A$ is the number of new infections that a male will cause in females of group j $(j = 1, 2)$ per unit of time;
- $b_m c_j \beta_{f_jm}^A$ is the number of new infections that a female in group j $(j = 1, 2)$ will cause in males per unit of time;
- $\frac{1}{\omega_i^A+\theta_i^A+\mu_i}$ $(i = m, f_1, f_2)$ represents the mean time that an individual in group i remains infected (i.e., in either A or L).

Thus, $\sqrt{\mathscr{R}^A_{mf_jm}}$ represents the average secondary HSV-2 male infections by one male individual through females in group j $(j = 1, 2)$ while in the infectious stage (A) in a completely susceptible population. The square root is associated with the fact that we need to consider both the male-to-female and female-to-male processes to obtain the number of secondary infections. The overall reproduction number $\mathscr{R}^A_0$ is an average of $\mathscr{R}^A_{mf_im}$ $(i = 1, 2)$.

Let $\mathscr{R}^H_0$ denote the basic reproduction number for HIV in the absence of HSV-2. Then

$$\mathscr{R}^H_0 = \sqrt{\left(\mathscr{R}^H_{mf_1m}\right)^2 + \left(\mathscr{R}^H_{mf_2m}\right)^2},$$

where

$$\mathscr{R}^H_{mf_jm} = \sqrt{\frac{b_{f_j}\beta^H_{mf_j}}{d^H_m + \mu_m} \cdot \frac{b_m c_j \beta^H_{f_jm}}{d^H_{f_j} + \mu_{f_j}}}, \quad j = 1, 2.$$

The biological meanings of $\mathscr{R}^H_{mf_1m}$ and $\mathscr{R}^H_{mf_2m}$ can be explained in the similar way as those of $\mathscr{R}^A_{mf_1m}$ and $\mathscr{R}^A_{mf_2m}$. It is clear that $\mathscr{R}^H_0$ represents the average secondary HIV male infections by one male individual (through both female groups) during the whole HIV infective period in a completely susceptible population.

8.6.2 Invasion Reproduction Numbers

Let $\mathscr{R}^H_A$ denote the invasion reproduction number for HIV in a population where the HSV-2 infection is already established at the endemic equilibrium, which is denoted by E^A_∂. The nonzero components of E^A_∂ are S^0_i, A^0_i, and L^0_i, representing the density of susceptible, acute HSV-2, and HSV-2 latent, respectively, in group i. Let $N^0_i = S^0_i + A^0_i + L^0_i$. For ease of notation, let

$$\lambda^{A0}_m = b_m \sum_{i=1}^{2} c_i \beta^A_{f_jm} \frac{A^0_{f_j}}{N^0_{f_j}}, \qquad \lambda^{A0}_{f_j} = b_{f_j}\beta^A_{mf_j}\frac{A^0_m}{N^0_m}, \quad j = 1, 2$$

and

$$\mathbf{d}_i = \left(1, \delta^P_i, \delta^Q_i\right), \qquad \mathbf{x}^0_i = \left(S^0_i, \delta^A_i A^0_i, \delta^L_i L^0_i\right)^T, \quad i = m, f_1, f_2.$$

Note that the system (8.26) has 9 infected variables with HIV $(H_i, P_i, Q_i, i = m, f_1, f_2)$. Consider the HIV-free equilibrium E^A_∂ of system (8.26). The matrices

$\mathscr{F}^H$ and $\mathscr{V}^H$ (corresponding to the new infection and remaining transfer terms, respectively) are given by

$$\mathscr{F}^H = \begin{pmatrix} 0 & F^H_{f_1 m} & F^H_{f_2 m} \\ F^H_{m f_1} & 0 & 0 \\ F^H_{m f_2} & 0 & 0 \end{pmatrix}, \qquad \mathscr{V}^H = \begin{pmatrix} V^H_m & 0 & 0 \\ 0 & V^H_{f_1} & 0 \\ 0 & 0 & V^H_{f_2} \end{pmatrix}, \tag{8.31}$$

where

$$F^H_{f_j m} = b_m c_j \beta^H_{f_j m} \frac{\mathbf{x}^0_m}{N^0_m} \mathbf{d}_{f_j}, \quad F^H_{m f_j} = b_{f_j} \beta^H_{m f_j} \frac{\mathbf{x}^0_{f_j}}{N^0_{f_j}} \mathbf{d}_m, \quad j = 1, 2$$

and

$$V^H_i = \begin{pmatrix} (\mu_i + d^H_i + \delta^H_i \lambda^{A0}_i) & 0 & 0 \\ -\delta^H_i \lambda^{A0}_i & \omega^P_i + \theta^P_i + \mu_i + d^P_i & -\gamma^Q_i(\theta^P_i) \\ 0 & -(\omega^P_i + \theta^P_i) & \gamma^Q_i(\theta^P_i) + \mu_i + d^Q_i \end{pmatrix}, \tag{8.32}$$

for $i = m, f_1, f_2$. Then, the next generation matrix for HIV, denoted by K_H, can be expressed by

$$\begin{aligned} K_H &= \mathscr{F}^H (\mathscr{V}^H)^{-1} \\ &= \begin{pmatrix} 0 & F^H_{f_1 m}(V^H_{f_1})^{-1} & F^H_{f_2 m}(V^H_{f_2})^{-1} \\ F^H_{m f_1}(V^H_m)^{-1} & 0 & 0 \\ F^H_{m f_2}(V^H_m)^{-1} & 0 & 0 \end{pmatrix} := \left(k_{ij}\right)_{9\times 9}, \end{aligned} \tag{8.33}$$

where the entries k_{ij} of the matrix K_H can be found in the Appendix A of [52].

Noting that $\mathrm{Rank}(K_H) = 2$ and that the sum of the diagonal elements in matrix K_H is zero, it follows from Vieta's formulas that if the numbers of susceptible people and those with acute and latent HSV-2 in group i are S^0_i, A^0_i, L^0_i, respectively, the reproduction number for HIV infection is given by

$$\begin{aligned} \mathscr{R}^H_A &= R^H_A(S^0_i, A^0_i, L^0_i, 0, 0, 0) := \rho(K_H) = \sqrt{-E_2(K_H)} \\ &= \sqrt{\sum_{i=1}^{3} \sum_{j=4}^{9} k_{ij} k_{ji}}, \end{aligned} \tag{8.34}$$

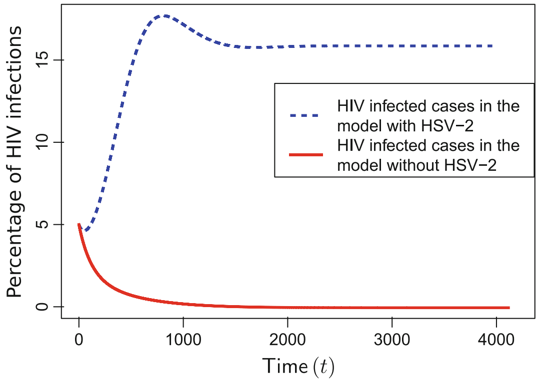

Fig. 8.7 Numerical solutions of the system (8.26) for the case when $\mathscr{R}_0^A > 1, \mathscr{R}_0^H < 1$, and $\mathscr{R}_A^H > 1$. The dashed and solid curves represent levels of HIV infections with and without HSV-2 present, respectively. It shows that even when the basic reproduction number for HIV $\mathscr{R}_0^H$ is less than 1, HIV can still persist if the invasion reproduction number $\mathscr{R}_A^H$ is greater than 1

where $\rho(K_H)$ represents the spectral radius of the matrix K_H and $E_2(K_H)$ is the sum of all the 2×2 principal minors of matrix K_H. It is shown in [52] that invasion is possible if and only if $\mathscr{R}_A^H > 1$.

Similarly, an invasion reproduction number $\mathscr{R}_H^A$ for HSV-2 to invade a population in which HIV is present (see [52]). Detailed results on the existence and local stability of the boundary equilibria can also be found in [52].

8.6.3 *Influence of HSV-2 on the Dynamics of HIV*

Figure 8.7 illustrates the result of numerical simulations showing how the joint disease dynamics of HIV and HSV-2 may depend on the basic and invasion reproduction numbers. It is for the case when enhancement of HIV by HSV-2 is relatively strong with $\mathscr{R}_0^A > 1, \mathscr{R}_0^H < 1$, and $\mathscr{R}_A^H > 1$. It shows that while HIV can invade and persist in the presence of HSV-2 (the dashed curve), it dies out in the absence of HSV-2 (the solid curve), suggesting that HSV-2 infection can favor the invasion of HIV.

8.7 An HIV Model with Vaccination

Blower et al. [15] studied model for HIV with live attenuated HIV vaccines (LAHVs). Consider two viral strains, one wild strain and one vaccine strain. Divide the total population into the following epidemiological classes: susceptible individuals (S), unvaccinated individuals infected with the wild-type HIV (I_w) or the vaccine strain (either by vaccination or by transmission) (I_v) or dually infected with both strains (I_{vw}), and individuals with AIDS (A). The model consists of the following ordinary differential equations:

$$
\begin{aligned}
S' &= (1-p)\pi - (c\lambda_v + c\lambda_W + \mu)S,\\
I_v' &= p\pi + c\lambda_v S - (1-\psi)c\lambda_w I_v - (\nu_v + \mu)I_v,\\
I_w' &= c\lambda_w S - (\nu_w + \mu)I_w,\\
I_{vw}' &= (1-\psi)c\lambda_w I_v - (\nu_{vw} + \mu)I_{vw},\\
A' &= \nu_w I_w + \nu_v I_v + \nu_{vw} I_{vw} - (\mu_A + \mu)A,
\end{aligned}
\tag{8.35}
$$

where λ_v and λ_w are per-capita risks of infection with the vaccine and wild-type strains, respectively, given by

$$\lambda_v = \beta_v \frac{I_v}{N_{SA}}, \quad \lambda_w = \beta_w \frac{I_w + gI_{vw}}{N_{SA}},$$

and $N_{SA} = X + I_v + I_w + I_{vw}$ denotes the number of sexually active population. Other parameters include: β_v and β_w are infection rates for vaccine and wild-type strains, respectively, p is the fraction of new susceptibles vaccinated, π is the number of new susceptibles that join the sexually active population per unit time, c is the average rate of acquiring new sex partners, $1/\mu$ is the average period of acquisition of new sex partners, $1/\mu_A$ is the average survival time with AIDS, ψ denotes the degree of protection that the vaccine provides against infection with the wild-type strain, ν is the progression rate to AIDS in individuals infected with the LAHV strain (ν_v), the wild-type strain (ν_w), or both strains (ν_{vw}), $1/\mu_A$ is the average survival time from AIDS to death. The disease progression rates are related by the expression $\nu_{vw} = \delta\nu_w$, where δ specifies the vaccine-induced degree of reduction in the wild-type disease progression rate.

A time-dependent uncertainty analysis of model (8.35) can be used [15] to predict the potential impact of LAHVs on the annual AIDS death rate, as illustrated in Fig. 8.8. It shows the result of infection with the wild-type strain of HIV for Zimbabwe (A) and Thailand (B), and the result of the LAHV strain for Zimbabwe (C) and Thailand (D). Parameter values used include the following probability density functions (pdfs): $1/\mu_A$ (pdf: 9 months to 1 year to 18 months), β_w (pdf: 0.05 to 0.1 to 0.2), $\beta_v = \alpha\beta_w$ where α (range of pdf: (0.001, 0.1)), ν_w (pdf: range from 50% progression to AIDS in 7.5 years to 50% progression in 10 years). Consider a mass vaccination campaign (with follow-up programs) that would vaccinate anywhere from 80% to 95% of susceptibles with p (range of pdf: (0.8, 0.95)), ψ (range of pdf: (0.5, 0.95)), δ (range of pdf: (0.1, 1)). The population size of sexually active adults are chosen to be 5,560,000 (Zimbabwe), 34,433,00 (Thailand).

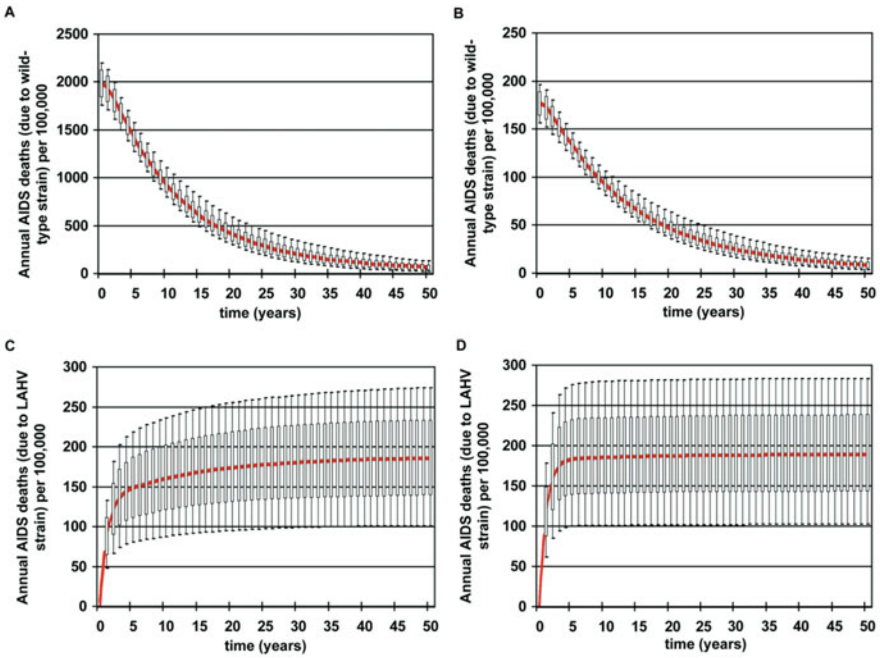

Fig. 8.8 Simulation results of model (8.35). It plots annual AIDS deaths (per 100,000 individuals) for Zimbabwe (**A**), Thailand (**B**), Zimbabwe (**C**), and Thailand (**D**). *Source*: [15]

8.8 A Model with Antiretroviral Therapy (ART)

A mathematical model with antiretroviral therapy (ART) is considered in [25] to study the effect of ART on risk behaviors and sexually transmitted infections (STI). Individuals are divided into two risk groups $i = 1, 2$, with $s = 1$ for STI+ and $s = 0$ for STI-. The population size for fix i and s is divided into the following epidemiological classes: susceptible to HIV (S_{is}), untreated HIV+ (I^u_{is}), untreated with AIDS (A^u_{is}), treated HIV+ (I^τ_{is}), treated with AIDS (A^τ_{is}). The group sizes are

$$N_{is} = S_{is} + I^u_{is} + I^\tau_{is} + A^\tau_{is}, \quad i = 1, 2, \ s = 0, 1.$$

The per-capita rates of STI and HIV infection of a susceptible individual in risk group i are denoted by $\xi_i(t)$ and $\lambda_{is}(t)$, respectively, and are given by

$$\xi_i(t) = \theta_i \sum_j \rho_{ij} \frac{N_{j1}}{\sum_s N_{js}}, \quad i = 1, 2, \tag{8.36}$$

$$\lambda_{i0}(t) = \beta_i \sum_{j=1}^{2} \rho_{ij} \frac{\sum_s \left(I^u_{js} + (1-\eta)(I^\tau_{js} + A^\tau_{js}) \right)}{\sum_s N_{js}}, \quad \lambda_{i1} = 3\lambda_{i0}, \qquad i = 1, 2, \tag{8.37}$$

where θ_i and β_i are transmission rates of STI and HIV, respectively, for susceptibles of risk level i, ρ_{ij} represents the sexual mixing between types i and j individual (e.g., proportionate mixing), η_1 represents the reduction in HIV infectiousness due to treatment with ART.

The following model is a simplified version of the model considered in [25]:

$$\begin{aligned}
\frac{dS_{is}}{dt} &= \Lambda_i - (\lambda_{is}(t) + \mu)S_{is} + (1-s)\big[-\xi_i(t)S_{i0} + \delta S_{i1}\big] + s\big[\xi_i(t)S_{i0} - \delta S_{i1}\big],\\
\frac{dI^u_{is}}{dt} &= \lambda_{is}(t)S_{is} - (\gamma^u + \mu + r^h)I^u_{is}\\
&\quad +\omega I^\tau_{is} + (1-s)\big[-\xi_i(t)I^u_{i0} + \delta I^u_{i1}\big] + s\big[\xi_i(t)I^u_{i0} - \delta I^u_{i1}\big]\\
\frac{dI^\tau_{is}}{dt} &= r^h I^u_{is} - (\gamma^\tau + \mu + \omega)I^\tau_{is}\\
&\quad +(1-s)\big[-\xi_i(t)I^\tau_{i0} + \delta I^\tau_{i1}\big] + s\big[\xi_i(t)I^\tau_{i0} - \delta I^\tau_{i1}\big] \qquad (8.38)\\
\frac{dA^u_{is}}{dt} &= \gamma^u I^u_{is} - (\alpha^u + \mu + r^a)A^u_{is} + \omega A^\tau_{is} + (1-s)\delta A^u_{i1} - s\delta A^u_{i1}\\
\frac{dA^\tau_{is}}{dt} &= \gamma^\tau I^\tau_{is} - (\alpha^\tau + \mu + \omega)A^\tau_{is}\\
&\quad +r^a A^u_{is} + (1-s)\big[-\xi_i(t)A^\tau_{i0} + \delta A^\tau_{i1}\big] + s\big[\xi_i(t)A^\tau_{i0} - \delta A^\tau_{i1}\big],
\end{aligned}$$

where $i = 1, 2, s = 0, 1$, Λ_i is the recruitment rate to group i ($i = 1, 2$), γ^u and γ^τ are the rates of progression to AIDS for untreated and treated individuals, respectively, α^u and α^τ are the rates of AIDS mortality for untreated and treated individuals, respectively, δ is the recovery rate from the STI infection, η represents the reduction in HIV infectiousness as a result of ART, w is the withdraw rate from treatment, r^a and r^h are treatment coverage rates of AIDS and HIV-positive individuals, respectively, $1/\mu$ represents the average duration of sexually active life.

A more general model is studied in [25], in which a detailed model analysis is presented to demonstrated the impact of the wide-scale use of ART on HIV transmission.

8.9 Project: What If Not All Infectives Progress to AIDS?

In the model (8.1) it is assumed that all HIV-infected individuals eventually progress to full-blown AIDS, as this appears to be the case. Suppose, however, that only a fraction $p, 0 < p < 1$ progress to AIDS while the remaining infectives remain in this class until they are no longer sexually active. In addition to the classes S, I, and A, a model must now also include a class Y of infective individuals that will not develop full-blown AIDS and a class Z of former Y-individuals who are no longer sexually active. The corresponding model is

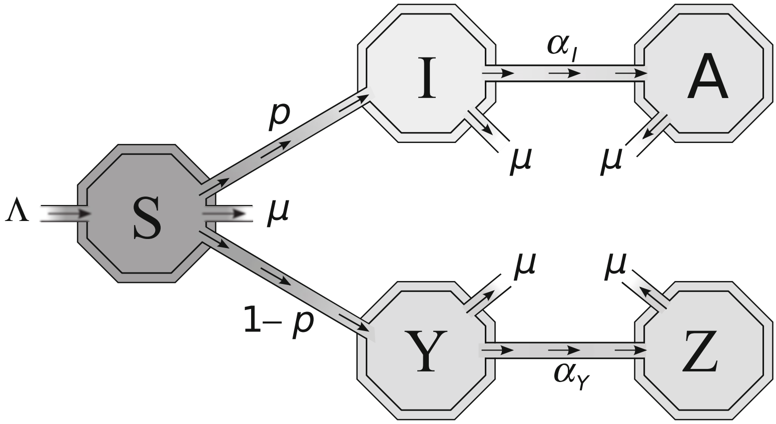

Fig. 8.9 Flow diagram; single group model for the case when only a fraction of infected people will progress to AIDS

$$
\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - \lambda C(T(t))\frac{S(t)W(t)}{T(t)} - \mu S(t)\\
\frac{dI(t)}{dt} &= \lambda p C(T(t))\frac{S(t)W(t)}{T(t)} - (\alpha_I + \mu)I(t)\\
\frac{dY(t)}{dt} &= \lambda(1-p)C(T(t))\frac{S(t)W(t)}{T(t)} - (\alpha_Y + \mu)Y(t)\\
\frac{dA(t)}{dt} &= \alpha_I I(t) - (d+\mu)A(t)\\
\frac{dZ(t)}{dt} &= \alpha_Y Y(t) - \mu Z(t)
\end{aligned}
\tag{8.39}
$$

where

$$W = I + Y \quad \text{and} \quad T = W + S. \tag{8.40}$$

A flow diagram is shown in Fig. 8.9.

It is further assumed that individuals who develop full-blown AIDS are no longer actively infective, that is, that they have no sexual contacts; it is also assumed that infected individuals become immediately infective. Finally, it is assumed that individuals in this population become sexually inactive or acquire AIDS at the constant rates α_Y and α_I (respectively) per unit time. Therefore, $1/(\mu + \alpha_I)$ gives the average or mean incubation period with the fraction $1/(\mu + \alpha_Y)$ denoting the average or mean sexual life expectancy. For simplicity, we assume $\alpha_I = \alpha_Y$, but it is possible to extend the model to the case $\alpha_i \neq \alpha_Y$.

As before, the function $C(T)$ models the mean number of sexual partners an average individual has per unit time when the population density is T; λ (a constant) denotes the average sexual risk per infected partner; λ is often thought as the product $i\phi$ [68], where ϕ is the average number of contacts per sexual partner and i the conditional probability of infection from a sexual contact when the latter is infected. Kingsley et al. [72] had presented (not surprising) evidence that the probability of seroconversion (infection) increases with the number of infected sexual partners. Hence, $\lambda C(T)$ models the transmission rate per unit time per infected partner when the size of the sexually active population is T. We continue to assume

$$C(T) > 0, \qquad C'(T) \geq 0, \tag{8.41}$$

Question 4 Show that for the model (8.39) the basic reproduction number is given by

$$\mathscr{R}_0 = \lambda \left(\frac{p}{\sigma_I} + \frac{1-p}{\sigma_Y} \right) C \left(\frac{\Lambda}{\mu} \right), \tag{8.42}$$

where $\sigma_I = \alpha_I + \mu$, $\sigma_Y = \alpha_Y + \mu$.

$\mathscr{R}_0$ is given by the product of the three factors (epidemiological parameters): λ (the probability of transmission per partner), $C(\Lambda/\mu)$ (the mean number of sexual partners that an average susceptible individual has per unit time when everybody in the population is susceptible), and

$$D = \left(\frac{p}{\sigma_I} + \frac{1-p}{\sigma_Y} \right). \tag{8.43}$$

The death-adjusted mean infective period is $D = pD_I + (1-p)D_Y$ with D_I and D_Y denoting the death-adjusted mean infective periods, $1/\sigma_I$ and $1/\sigma_Y$ of the I and Y classes, respectively.

Question 5 Show that if $\mathscr{R}_0 < 1$, the disease-free equilibrium $(\Lambda/\mu, 0, 0)$ of the system (8.39) is asymptotically stable, and if $\mathscr{R}_0 > 1$ there is a unique endemic equilibrium (S^*, I^*, Y^*), which is locally asymptotically stable, and the disease-free state $(\Lambda/\mu, 0, 0)$ is unstable.

Next, we allow arbitrary incubation period distributions by introducing two functions $P_I(s)$ and $P_Y(s)$ representing the proportion of individuals who become I- or Y-infective at time t and that, if alive, are still infective at time $t+s$ (survive as infectious). P_I and P_Y, survivorship functions, are non-negative and non-increasing, and $P_I(0) = P_Y(0) = 1$. It is further assumed that

$$\int_0^\infty P_I(s)ds < \infty, \qquad \int_0^\infty P_Y(s)ds < \infty,$$

and thus, $-\dot{P}(x)$ and $-\dot{P}_Y(x)$ are the rates of removal of individuals from classes I and Y into classes A and Z, x time units after infection.

Question 6 Derive the corresponding model and determine its basic reproduction number.

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