

# DYNAMIC PARTNERSHIPS AND HIV TRANSMISSIONS BY STAGE

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For my mother,  
Jeom-im Yang

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# TABLE OF CONTENTS

<b>DEDICATION</b> . . . . .	<b>ii</b>
<b>ACKNOWLEDGEMENTS</b> . . . . .	<b>iii</b>
<b>LIST OF FIGURES</b> . . . . .	<b>vii</b>
<b>LIST OF TABLES</b> . . . . .	<b>ix</b>
<b>LIST OF ABBREVIATIONS</b> . . . . .	<b>x</b>
<b>ABSTRACT</b> . . . . .	<b>xi</b>
<b>CHAPTER</b>	
<b>I. Introduction</b> . . . . .	<b>1</b>
1.1 Modeling infection transmission . . . . .	1
1.2 How transmission models are formulated . . . . .	2
1.2.1 Deterministic compartmental models (DCMs) . . . . .	3
1.2.2 Individual-based models (IBMs) . . . . .	4
1.2.3 Network models . . . . .	5
1.3 Aspects of transmission models . . . . .	7
1.3.1 Contacts . . . . .	7
1.3.2 Basic reproductive ratio, $\mathcal{R}_0$ . . . . .	8
1.3.3 Endemic prevalence . . . . .	9
1.4 HIV and AIDS . . . . .	10
1.4.1 The identification of HIV/AIDS . . . . .	10
1.4.2 The AIDS epidemics . . . . .	11
1.4.3 How HIV/AIDS works . . . . .	11
1.4.4 Clinical course of HIV infection . . . . .	12
1.5 Dissertation overview . . . . .	15
<b>II. Effects of Sexual Partnerships on HIV Transmissions by Stage</b> . . . . .	<b>17</b>
2.1 Abstract . . . . .	17
2.2 Introduction . . . . .	18
2.3 Methods . . . . .	20
2.3.1 The natural history of HIV infection . . . . .	20
2.3.2 Compartmental flows for the model analyzed . . . . .	21
2.3.3 Partnership formation . . . . .	22
2.3.4 Partnership dissolution . . . . .	23
2.3.5 Probability of infection . . . . .	23
2.3.6 Model simulation . . . . .	23
2.4 Results . . . . .	24

2.4.1	Partnership duration varies while average number of partners does not . . . . .	25
2.4.2	Average number of partners as well as partnership duration is varied. . . . .	30
2.4.3	Partnership concurrency at a given average number of partners as well as partnership duration is varied . . . . .	34
2.5	Discussion . . . . .	37
<b>III. Effects of Sexual Partnership Dynamics on HIV Transmissions by Stage . . . . .</b>		<b>41</b>
3.1	Abstract . . . . .	41
3.2	Introduction . . . . .	42
3.3	Methods . . . . .	45
3.3.1	Compartmental flows for the model analyzed. . . . .	45
3.3.2	Duration of infection and transmission probability . . . . .	45
3.3.3	Pair approximation . . . . .	47
3.3.4	The $SI$ model . . . . .	47
3.3.5	The $SI_1I_2$ model . . . . .	50
3.3.6	Correlation and average number of partners . . . . .	51
3.3.7	Background removal . . . . .	52
3.4	Results . . . . .	52
3.4.1	The $SI$ model . . . . .	52
3.4.2	The $SI_1I_2$ model . . . . .	57
3.4.3	Endemic prevalence and the fraction of transmissions from PHI at endemic phase . . . . .	61
3.4.4	Endemic prevalence and the fraction of transmissions from PHI at endemic phase with background removal . . . . .	63
3.5	Discussion . . . . .	64
<b>IV. Sexual Role Segregation and HIV Transmissions by Stage . . . . .</b>		<b>67</b>
4.1	Abstract . . . . .	67
4.2	Introduction . . . . .	68
4.3	Methods . . . . .	69
4.3.1	Compartmental flows for the model analyzed . . . . .	69
4.3.2	Duration of infection and transmission probability . . . . .	70
4.3.3	Pair approximation . . . . .	72
4.3.4	The $SI$ model . . . . .	72
4.3.5	The $SI_1I_2$ model . . . . .	75
4.3.6	Correlation and average number of partners . . . . .	76
4.3.7	Background removal . . . . .	78
4.3.8	Algebraic calculation and numerical integration . . . . .	78
4.4	Results . . . . .	78
4.4.1	$\mathcal{R}_0$ for the $SI$ model . . . . .	78
4.4.2	$\mathcal{R}_0$ for the $SI_1I_2$ model . . . . .	85
4.4.3	$\mathcal{R}_0$ and the fractional contribution to $\mathcal{R}_0$ of PHI between the extremes of instantaneous and fixed partnerships . . . . .	87
4.4.4	Endemic prevalence and the fraction of transmissions from PHI at endemic phase . . . . .	89
4.4.5	Endemic prevalence and the fraction of transmissions from PHI at endemic phase with background removal . . . . .	90
4.5	Discussion . . . . .	91
<b>V. High-Risk Behaviors and HIV Transmissions by Stage . . . . .</b>		<b>93</b>

5.1	Abstract . . . . .	93
5.2	Introduction . . . . .	94
5.3	Methods . . . . .	96
	5.3.1 Natural history of HIV infection . . . . .	96
	5.3.2 Compartmental flows for the model analyzed . . . . .	96
	5.3.3 Partnership dynamics . . . . .	97
	5.3.4 Average number of partners . . . . .	98
	5.3.5 Probability of infection . . . . .	99
	5.3.6 Model Simulation . . . . .	100
	5.3.7 Simulation scenarios . . . . .	101
	5.3.8 Control programs . . . . .	103
5.4	Results . . . . .	104
	5.4.1 Effects of risk behavior change on endemic prevalence . . . . .	104
	5.4.2 Effects of risk behavior change on the fraction of transmissions from PHI . . . . .	104
	5.4.3 Effects of risk behavior change on the average number of secondary cases . . . . .	108
	5.4.4 Effects of risk behavior change on control program effects . . . . .	110
5.5	Discussion . . . . .	112
<b>VI. Conclusions and Future Study . . . . .</b>		<b>115</b>
6.1	Summary . . . . .	115
	6.1.1 $\mathcal{R}_0$ and endemic prevalence . . . . .	116
	6.1.2 The fraction of transmissions from PHI . . . . .	117
	6.1.3 DCMs with pair approximation . . . . .	119
	6.1.4 IBMs . . . . .	120
6.2	Suggestions for future research . . . . .	121
	6.2.1 Robustness assessment . . . . .	121
6.3	Implications of our research . . . . .	122
	6.3.1 Evaluating the effectiveness of HIV control programs . . . . .	122
	6.3.2 Understanding HIV transmissions in a complex situation . . . . .	123
<b>APPENDIX . . . . .</b>		<b>125</b>
<b>BIBLIOGRAPHY . . . . .</b>		<b>127</b>

## LIST OF FIGURES

### Figure

1.1	The typical course of HIV infection. . . . .	13
1.2	Transmission probability per sex act over the course of HIV infection. . . . .	14
2.1	Compartmental flows for the model analyzed. . . . .	21
2.2	Endemic prevalence and the fraction of $S-I$ pairs out of total pairs across partnership duration. . . . .	25
2.3	Fraction of transmissions from PHI and the fraction of $S-P$ pairs out of all $S-I$ pairs across partnership duration. . . . .	26
2.4	Fraction of $S-P$ pairs out of originally discordant $S-I$ pairs and out of $S-I$ pairs that were originally concordantly susceptible across partnership duration. . . . .	27
2.5	Compartmental flows among discordant pairs. . . . .	29
2.6	Expected fraction of $S-P$ pairs as a function of time elapsed after pair formation. . . . .	30
2.7	Fraction of $S-I$ pairs that were originally discordant or that were originally concordantly susceptible out of total $S-I$ pairs. . . . .	31
2.8	Endemic prevalence across partnership duration at four levels of $Q$ . . . . .	32
2.9	Fraction of transmissions from PHI across partnership duration at four levels of average number of partners, $Q$ . . . . .	33
2.10	Fraction of $S-P$ pairs out of total $S-I$ pairs across partnership duration at four levels of average number of partners, $Q$ . . . . .	34
2.11	Expected fraction of $S-P$ pairs as a function of time elapsed after pair formation at four levels of average number of partners. . . . .	35
2.12	Degree distribution at four levels of $\theta$ . . . . .	36
2.13	Endemic prevalence across partnership duration at four levels of $\theta$ . . . . .	37
2.14	Fraction of transmissions from PHI across partnership duration at four levels of $\theta$ . . . . .	38
2.15	Fraction of $S-P$ pairs out of total $S-I$ pairs across partnership duration at four levels of $\theta$ . . . . .	39
3.1	Compartmental flows for the model analyzed. . . . .	45
3.2	Results from pair approximation and the average of 100 stochastic simulations. . . . .	53
3.3	Quasi-equilibrium values of the correlation between susceptible and infected individuals, $C_{SI}^*$ , and basic reproductive ratio, $\mathcal{R}_0$ , across partnership duration and transmission rate. . . . .	55
3.4	Fraction of population infected over time across different transmission rate, $\beta$ , and the duration of infection, $1/\gamma$ , given that $\beta/\gamma$ remains constant. . . . .	56
3.5	Quasi-equilibrium values of the correlation with susceptibles during PHI or chronic stage and the fractional contribution to $\mathcal{R}_0$ of PHI across partnership duration. . . . .	59
3.6	Basic reproductive ratio, $\mathcal{R}_0$ , and the fractional contribution to $\mathcal{R}_0$ of PHI across partnership duration and average number of partners. . . . .	60
3.7	Endemic prevalence and the fraction of transmissions from PHI at endemic phase across variable durations and numbers of partnerships. . . . .	62
3.8	Endemic prevalence and fraction of transmissions from PHI at endemic phase with background removal across variable durations and numbers of partnerships. . . . .	62
4.1	Compartmental flows for the model analyzed. . . . .	70
4.2	Results from pair approximation and the average of 100 stochastic simulations. . . . .	80



4.3	Quasi-equilibrium values for the correlation between susceptible and infected individuals under various average numbers of partners and average transmission rates.	83
4.4	Product of quasi-equilibrium values for the correlation between susceptible and infected individuals and $\mathcal{R}_0$ under various average number of partners and average transmission rates.	83
4.5	Product of correlations and $\mathcal{R}_0$ across partnership duration and the ratio of transmission rates (male-to-female to female-to-male).	84
4.6	$\mathcal{R}_0$ across partnership duration, average number of partners, and ratio of transmission rates (male-to-female to female-to-male).	88
4.7	Fractional contribution to $\mathcal{R}_0$ of PHI across partnership duration, average number of partners, and ratio of transmission rates (male-to-female to female-to-male).	88
4.8	Endemic prevalence across partnership duration, average number of partners, and ratio of transmission rates (male-to-female to female-to-male).	89
4.9	The fraction of transmissions from PHI across partnership duration, average number of partners, and ratio of transmission rates (male-to-female to female-to-male)	90
4.10	Endemic prevalence across partnership duration, average number of partners, and ratio of transmission rates (male-to-female to female-to-male) with background removal.	91
4.11	The fraction of transmissions from PHI across partnership duration, average number of partners, and ratio of transmission rates (male-to-female to female-to-male) with background removal.	92
5.1	Compartmental flows for the model analyzed.	96
5.2	Endemic prevalence at three different rates of risk behavior change as the rate of partner change in high-risk phase is varied.	105
5.3	Fraction of transmissions from PHI at three different rates of risk behavior change as the rate of partner change in high-risk is varied.	106
5.4	Fraction of individuals with PHI at three different rates of risk behavior change as the rate of partner change in high-risk phase is varied.	107
5.5	Average number of secondary cases by an index case who is infected in high-risk phase as the rate of partner change in high-risk is varied.	108
5.6	Average number of secondary cases by an index case infected by individuals with PHI as the rate of partner change in high-risk is varied.	110
5.7	Effectiveness of reducing transmissions from PHI or post-PHI	111
5.8	Endemic prevalence and the fraction of transmissions from PHI for different $\theta$ as the rate of partner change in high-risk is varied.	112

## LIST OF TABLES

### Table

1.1	Summary for the chapters followed . . . . .	16
2.1	Model Parameters . . . . .	21
3.1	Model parameters. For the <i>SI</i> model, $\beta$ and $\gamma$ are used without the subscript. . . . .	46
3.2	State variables for the model . . . . .	47
4.1	Model parameters. In the <i>SI</i> model, $\beta_{ijk}$ and $\gamma_k$ are used without subscript $k$ . . . . .	70
5.1	Model parameters. Probabilities are defined per day. . . . .	101

## LIST OF ABBREVIATIONS

- AIDS** Acquired immunodeficiency syndrome
- DCM** Deterministic compartmental model
- HIV** Human immunodeficiency virus
- HTLV-III** Human lymphotropic virus III
- IBM** Individual-based model
- LAV** Lymphadenopathy-associated virus
- MCA** Moment closure approximation
- NCI** National Cancer Institute
- ODE** Ordinary Differential Equation
- PA** Pair approximationPDEPartial Differential Equation
- PHI** Primary HIV infection
- SIV** Simian immunodeficiency virus

## ABSTRACT

Dynamic Partnerships and HIV Transmissions by Stage

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Effectiveness of some control programs of human immunodeficiency virus (HIV) transmission depends on what proportion of new infections are attributable to a particular stage of HIV infection. Most model analyses for the transmission of HIV by stage have neglected real-world details such as sexual partnerships, risk fluctuation and sexual role segregation. To examine the effects of those real-world details on the transmission of HIV by stage, we constructed various models of HIV transmission using both individual-based and deterministic compartmental approaches.

Transmissions through long-term sexual partnerships generate local network structure in which infected individuals are connected to fewer susceptible partners compared with the population average. The increasing depletion of susceptible partners around infected individuals monotonically decreases basic reproductive ratio,  $\mathcal{R}_0$ , and endemic prevalence of HIV infection with increasing partnership duration. The role of primary HIV infection (PHI), i.e., fractional contribution to  $\mathcal{R}_0$  of PHI or the fraction of transmissions from PHI at endemic phase, has a U-shaped relationship with partnership duration. It drops in shorter partnerships, but rises in longer partnerships. This pattern is determined by the difference in relative depletion of susceptible

partners by stage of infection. As the risk of transmission is made increasingly different by type of sex act while keeping the total population risk unchanged, endemic prevalence and the role of PHI become smaller. The decreased role of PHI is only observed when partnerships are long lasting. If individuals fluctuate between high- and low-risk phases, susceptible individuals are replenished from low- to high-risk phase and infection is spread from high- to low-risk phase. This increases endemic prevalence in the overall population. Risk fluctuation also causes individuals with PHI to be more likely to be in high-risk phase, which increases the role of PHI.

Realistic details like sexual partnerships, sexual role segregation and risk fluctuation can strongly influence the transmission of HIV and do so differentially by stage of HIV infection. Model analyses intended to evaluate control program options or assess the role of a particular stage of infection need to take these details into account.

## CHAPTER I

### Introduction

#### 1.1 Modeling infection transmission

Modeling infection transmission is useful in several broad perspectives, which are not necessarily exclusive. To begin with, building a mathematical structure of what is already understood from empirical knowledge often leads the modeler to examine the underlying assumptions about transmission and to understand what is at work. Also, well-constructed models are useful to predict the course of an epidemic in a real population. Models can be used to assess the relative effectiveness of strategies to control the spread of infection, such as vaccination, treatment, quarantine, education about specific behaviors to reduce transmission, etc. Another important point is that, through the analyses of the constructed models, the modeler gains insight into the transmission system, which then leads to improvement of the science of infection transmission in general. Finally, transmission models are useful to analyze data. Data on infection transmission can be better analyzed by the model capturing processes that generated data than by standard statistical models that do not refer to the processes at work.

Our ultimate goal is to analyze human immunodeficiency virus (HIV) genetic sequence data to make useful predictions such as effectiveness of strategies to control

HIV spread. This thesis is, however, the first step toward our ultimate goal. In it, we seek to identify what real-world details are more important than others in the transmission of HIV and understand how those details interact with one another. In particular, we focus on dynamic sexual partnerships, sexual role segregation, and risk behavior change. We examine how those aspects influence endemic levels of HIV infection and the fraction of transmissions at endemic phase that arise from primary HIV infection (PHI).

Transmission models, also called “models of systems” or “models of process” in physiology [1], are built up by describing the basic processes at work in a system. They relate individuals to each other using parameters that express contact rates or transmission probabilities. They are formulated using mathematics by implementing the essential features of the transmission system.

This way of modeling is better understood by comparing with traditional statistical models. Statistical models such as linear regression models estimate parameters that relate exposure to disease in individuals [2]. These models, called “models of data” in physiology [1], are chosen to fit particular data sets without reference to the processes at work in the system. One of the fundamental assumptions of these models is the independence between the outcomes of individuals, which is not appropriate for infection transmission.

## **1.2 How transmission models are formulated**

Transmission models can be divided depending on how one describes infection transmission in a population. One common approach is to classify individuals depending on their states (e.g., infection status) and to describe how the number (or the fraction) of individuals in each state changes over time. This is sometimes

called state-variable models [3]. Another approach is to model individuals as discrete entities and this class of models is called “individual-based models (IBMs)”. Finally, there is a class of models called “network models” that might fall between state-variable models and IBMs. In this thesis, we use all three types of modeling approaches and it is essential for appreciating the implications of our study to understand the basic assumptions for each type of model. Therefore, for the next few sections, we describe these different modeling approaches in some detail.

### 1.2.1 Deterministic compartmental models (DCMs)

The state-variable models are also called compartmental models, which we will use in this thesis. A compartmental model is made up of a finite number of compartments, each of which consists of homogeneous and “well-mixed” individuals [4]. Individuals in different compartments usually have different infection status, risk status, and so on. There can be flows into, out of, and between compartments and rules governing those flows are defined, which are usually expressed with ordinary differential equations (ODEs). These models are called deterministic compartmental models (DCMs) since infection outcomes in those models are not subject to chance.

A classic example of DCMs is the *SIR* model, which is also the most studied class of transmission models. In the *SIR* model, a population is divided into three compartments: susceptible (*S*), infective (*I*), and recovered (*R*). It appears that the *SIR* model was first extensively studied by Kermack and McKendrick in late 1920s and 1930s [5, 6, 7, 8, 9]. They looked at a situation where individuals are initially equally susceptible to a disease and a complete immunity is conferred by a single infection. In a special case where the rate of recovery,  $\gamma$ , and the rate of infectivity,  $\lambda$ , are constant, their equations for the epidemic can be represented, with



slight modifications of terms, as follows:

$$\begin{aligned}\frac{d}{dt}S &= -\lambda IS/N, \\ \frac{d}{dt}I &= \lambda IS/N - \gamma I, \\ \frac{d}{dt}R &= \gamma I,\end{aligned}\tag{1.1}$$

where  $S$ ,  $I$ , and  $R$ , denote the number of individuals who are susceptible, infective, removed, respectively. The last equation is redundant when we assume that total population size,  $N = S + I + R$ , remains constant.

These DCMs often provide elegant analytic descriptions about infection transmission in a population, such as the basic reproductive ratio,  $\mathcal{R}_0$ , which will be described in some detail in 1.3.2.

A fundamental assumption in Eqs. (1.1) is that individuals are well-mixed. That is, every individual in the population has the equal chance to contact and spread the disease to every other individual. This assumption is clearly not realistic. In the following sections, we describe models in which we can relax this assumption.

### 1.2.2 Individual-based models (IBMs)

Recent popularity of individual-based models (IBMs) is partly because of the development of high-power computers. In IBMs, one describes individuals as discrete entities and defines rules about how each individual interacts with one another. Here rules are flexible and so we can relax the well-mixed assumption. IBMs are often more intuitive than DCMs. For example, sexual transmission of HIV is more easily conceptualized with discrete individuals interacting with one another following a certain set of rules than with differential equations used in DCMs.

On the other hand, any behavior emerged from IBMs is influenced by many factors and sometimes it is hard to chase down what causes the behavior we see. Thus,

sometimes one cannot say whether the behavior we see is reasonable or not [10]. This lack of clarity can be a major drawback of IBMs. Also, IBMs are realized as stochastic simulations, which takes more time than numerical integrations used in DCMs.

### 1.2.3 Network models

A network, also called a *graph* in mathematics, is made up of *nodes* or *vertices*, and lines connecting them, usually called *edges*. In social literature, nodes and edges are often called *actors* and *relations*, respectively. In epidemiology, specifically for the transmission of sexually transmitted disease, *individuals* and their sexual *partnerships* may be more intuitive terms, which we use in this thesis.

In the network model, in general, each individual has a few partnerships through which a disease can spread. Since any one individual can only infect their immediate partners, the well-mixed assumption does not hold. That is, infection outcome of an individual becomes dependent on their immediate partners. Accordingly, correlation between individuals arise. For example, individuals are more likely to be infected when their partners are also infected, as opposed to when their partners are susceptible. This is more realistic than the well-mixed assumption.

Many network models ignore population and partnership turnover while infection spreads. That is, the only dynamic process in the model is infection transmission. We refer to these models as “fixed” network models. Fixed network models may be appropriate for modeling simple epidemics such as influenza, where the time scale of an epidemic is short compared with the other time scales of the system. Using fixed network models, a number of important characteristics about infection transmission in a population such as the distribution of the size of outbreaks have been derived [11].

To model endemic diseases, however, one needs to specify a continuous source of

new susceptible individuals. In addition, sexual partnerships of individuals are likely to change over the course of HIV infection since infection with HIV spans a long period of time. This implies fixed network models may not be best for modeling sexual transmission of HIV. Therefore we choose to use IBMs to model sexual transmission of HIV on networks where partnerships form and break. We will call them “dynamic” network models.

Also, there are ways to approximate infection transmissions on dynamic network models using ODEs. One way is to use moment closure approximation (MCA), which we use in this thesis. We describe MCA in the next section.

#### **Moment closure approximation (MCA)**

Moment closure approximation (MCA) is a method originally developed in solid-state physics [12] (cited in [13]). It is a deterministic approximation to a network model or some other spatial model such as partial differential equation (PDE) models or cellular automata. In the field of ecology and epidemiology, MCA has been extensively studied by several scholars at Warwick [10, 14, 15, 16].

To derive a moment closure approximation, the correlations between individuals (e.g., disease status) is treated as dynamic variables and equations are derived to track their time evolution. State variables in MCAs can be pairs of individuals of a certain type, or triples, etc [10]. Typically, when deriving the equations of motion at the  $n$ th level of correlation, terms including the  $(n + 1)$ th level of correlation will appear in the derivation. The resulting high level of correlation must either be retained as state variables or approximated in terms of lower-order correlations. The latter procedure is known as *moment closure*. In this thesis, we exclusively use moment closure at the pair level (i.e., *pair approximation*). In pair approximation, the number of triples is expressed in terms of the number of pairs.

The benefit of using MCA is that it provides a deterministic description that can incorporate the network structure that well-mixed models ignore. On the other hand, MCA ends up with a larger system of equations than the well-mixed model. Another drawback of MCA is the impossibility of obtaining exact expressions for error associated with the closure, which requires the modeler to carry out stochastic simulations of the network model being approximated and evaluate the goodness of the approximation [13].

### 1.3 Aspects of transmission models

#### 1.3.1 Contacts

In modeling infection transmission, a contact can refer to two types of events—the actual event of a transmission opportunity and the partnership between two individuals during which several such opportunities can arise [17]. For sexually transmitted infections like HIV, the former may indicate a sex act with an infected individual and the latter entering a partnership with another individual. In this thesis, we will use the terms a *sex act* and a (sexual) *partnership* instead of a contact.

In the class of well-mixed models, these two aspects of a contact are often modeled as a single instantaneous event. In this thesis, we treat them separate, which is an important aspect of our models of HIV transmission. Therefore, we use parameters indicating the frequency of partnership formation and dissolution per unit time as well as the frequency of sex acts during partnerships per unit time. For the frequency of sex acts per unit time, however, we sometimes use the term transmission rate instead. Transmission rate indicates the product of the frequency of sex acts per unit time and the transmission probability per sex act.

### 1.3.2 Basic reproductive ratio, $\mathcal{R}_0$

If one or more infected people are introduced into a community of individuals, under what conditions will an epidemic occur? This is one of the fundamental questions in epidemiology and is answered mainly using the basic reproductive ratio,  $\mathcal{R}_0$ .  $\mathcal{R}_0$  is defined as the average number of secondary cases produced by an infectious individual in an entirely susceptible population during that individual's period of infectiousness [18]. It is naturally considered as a threshold criterion, i.e., if  $\mathcal{R}_0 > 1$ , the epidemic occurs and otherwise the epidemic dies out.

The fundamental insight behind  $\mathcal{R}_0$  was discovered by Ross in 1909 [19]. He showed the existence of a quantity which, when less than unity, implies the disappearance of malaria from the population through a mathematical model.

In the well-mixed model,  $\mathcal{R}_0$  is constructed as the product of the mean duration of infection, the mean transmission probability, and the mean number of contacts [20]. For example,  $\mathcal{R}_0$  in the Kermack-McKendrick model presented in Eq. (1.1) is  $\lambda/\gamma$ , where  $\lambda$  is the product of mean transmission probability and number of contacts and  $1/\gamma$  is the mean duration of infection. In the network model considered in this thesis, however, a more sophisticated approach is required, which is described in Chapters 3 & 4.

We can derive several useful quantities from  $\mathcal{R}_0$  in the well-mixed model. As mentioned earlier, endemic and epidemic thresholds occur when  $\mathcal{R}_0 = 1$ . When there is a recurring source of susceptibles, the endemic level of infection is  $1 - 1/\mathcal{R}_0$ . In an *SIR* model described in Eq. (1.1), the epidemic eventually dies out with some proportion of susceptibles,  $S_\infty$ , which is given as a solution to  $S_\infty = \exp((S_\infty - 1)\mathcal{R}_0)$ . If the proportion of susceptible is lower than some threshold value  $S_T = 1/\mathcal{R}_0$ , then the disease can not invade the population. Thus the effective vaccination program needs

to lower the proportion of susceptibles below the threshold  $S_T$ .

### 1.3.3 Endemic prevalence

In epidemiology, an infection is said to be *endemic* when infection is constantly present with a given geographic area or population [21]. In this thesis, we use the term *endemic prevalence* (of infection) to indicate infection levels while being endemic. Specifically, the endemic prevalence is the infection level after a dynamic system, which is our transmission model, reaches a stationary point.

For an infection to be endemic, there has to be a recurring source of infection. For example, one of the simplest model for endemic infection can be obtained by modifying the *SIR* model (1.1) to *SIS* model. That is, we assume that individuals become susceptible again after passing the infectious period. Thus, following equations can describe an infection transmission system where infection can be endemic:

$$\begin{aligned}\frac{d}{dt}S &= -\lambda IS/N + \gamma I, \\ \frac{d}{dt}I &= \lambda IS/N - \gamma I.\end{aligned}\tag{1.2}$$

As before,  $S$  and  $I$  indicate the number of susceptible and infective individuals, respectively. We also assume the total population size,  $N = S + I$ , remains constant.

At a stationary point of the system,  $\frac{d}{dt}I = 0$ . Therefore,  $I^* = 0$  or  $\lambda S^*/N - \gamma = 0$ , where  $i^*$  indicates the quantity of  $i$  at a stationary point. Thus, the *fraction* of population infected is either 0 or  $1 - \gamma/\lambda$  ( $= 1 - S^*/N$ ). We saw that  $\lambda/\gamma = \mathcal{R}_0$  and so endemic prevalence (i.e., non-trivial infection level at a stationary point) is  $1 - 1/\mathcal{R}_0$  for  $\mathcal{R}_0 > 1$ .

Alternatively, we can argue that the following relation should hold at a stationary point:

$$\mathcal{R}_0 \mathcal{S}^* = 1,\tag{1.3}$$

where  $\mathcal{S}^*$  denotes the *fraction* of susceptible at a stationary point. Recall that  $\mathcal{R}_0$  indicates the number of secondary cases per index case given that all the “contacts” of the infected individual are made with susceptibles. Thus,  $\mathcal{R}_0\mathcal{S}^*$  indicates the number of secondary case per index case at a given fraction of susceptibles  $\mathcal{S}^*$  and should equal one for an infection level to become stationary.

Therefore, endemic prevalence,  $\mathcal{I}^*$ , is

$$\mathcal{I}^* = 1 - \mathcal{S}^* = 1 - 1/\mathcal{R}_0. \quad (1.4)$$

The relationship between  $\mathcal{R}_0$  and endemic infection level, however, relies on assumption that infected and susceptible individuals are well-mixed and thus does not hold in the model with partnerships or in heterogeneous populations. For that reason, we numerically integrate the equations or do stochastic simulations to find endemic prevalence of infections.

## 1.4 HIV and AIDS

Although our models are abstract and so can be adapted to various agents with few modifications, our intentions were to generate a framework related to understanding HIV transmission among populations. Therefore, we provide brief background information on HIV/AIDS.

### 1.4.1 The identification of HIV/AIDS

Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV). The name—acquired immunodeficiency syndrome, acronym AIDS—was agreed in Washington in July 1982. The name AIDS describes the disease accurately: people acquire the condition; it results in a deficiency within the immune system; and it is a syndrome not a single disease.

In 1983 the virus was first identified by the Institut Pasteur in France, which called it Lymphadenopathy-Associated Virus (LAV) [22]. In April 1984 in the U.S., the National Cancer Institute (NCI) isolated the virus and named it human T-lymphotropic virus-III (HTLV-III). In 1987 the name *human immunodeficiency virus* was confirmed by the International Committee on Taxonomy of Viruses.

#### **1.4.2 The AIDS epidemics**

As of 2007, there were 33.2 million people around the world living with HIV and among them 2.5 million people became newly infected in 2007. Every day, over 6800 persons become infected with HIV and over 5700 persons die from AIDS, mostly because of inadequate access to HIV prevention and treatment services [23]. Sub-Saharan Africa remains the most affected region in the global AIDS epidemic. More than two thirds (68%) of all people HIV-positive live in this region where more than three quarters (76%) of all AIDS deaths in 2007 occurred. Unlike other regions, the majority of people living with HIV in sub-Saharan Africa (61%) are women [23].

#### **1.4.3 How HIV/AIDS works**

There are two main sub-types of the virus: HIV-1 and HIV-2, the latter being harder to transmit and slower-acting. Both originate in simian (monkey) immunodeficiency virus (SIV) found in Africa. How and when the virus crossed the species barrier is still debatable. One hypothesis is that the epidemic has its origins through chimpanzee and monkey blood entering people's bodies possibly during the butchering of bush meat in the early and mid-20th century [24].

HIV attacks the cells of the immune system and, in particular, CD4<sup>+</sup> T cells, which organize body's overall immune response to foreign bodies and infections. The virus also attacks macrophages which engulf foreign invaders in the body. Inside



these cells, HIV produces more virus particles by converting viral RNA into DNA and then making many RNA copies. The conversion from RNA to DNA makes combatting HIV difficult. This is because this conversion is done by the enzyme called reverse transcriptase that lacks *proofreading*, which increases the chance of mutation. HIV mutation may mean it becomes a less of a killer, but equally it could become more robust and easily transmitted. Also, they become resistant to drugs through mutation.

The four major routes of HIV transmission are unprotected sexual intercourse, contaminated needles, breast milk, and transmission from an infected mother to her baby at birth. The majority of HIV infections are acquired through unprotected sexual relations, which is the focus of this thesis.

#### **1.4.4 Clinical course of HIV infection**

Infection with HIV-1 is associated with a progressive increase in viral load and an accompanying decrease of the CD4<sup>+</sup> T cells in the blood. HIV infection has basically four stages: incubation period, primary HIV infection (PHI), asymptomatic stage and late stage including AIDS.

The initial incubation period upon infection is asymptomatic and usually lasts between one and four weeks.

The second stage, PHI, which lasts an average of 4 weeks, is a period of rapid viral replication leading to virus in the peripheral blood with levels of HIV commonly approaching several million viruses per mL [25]. This response is accompanied by a marked drop in the numbers of circulating CD4<sup>+</sup> T cells [26, 27, 28, 29, 30]. During this period most individuals experience symptoms including fever, lymphadenopathy (i.e., swollen lymph nodes), pharyngitis (i.e., sore throat), rash, myalgia (i.e., muscle pain), malaise, and mouth and esophageal sores. Because of the nonspecific nature

of these symptoms, they are often not recognized as signs of HIV infection. However, recognizing the syndrome can be important because transmission during this period is readily occurred [31].

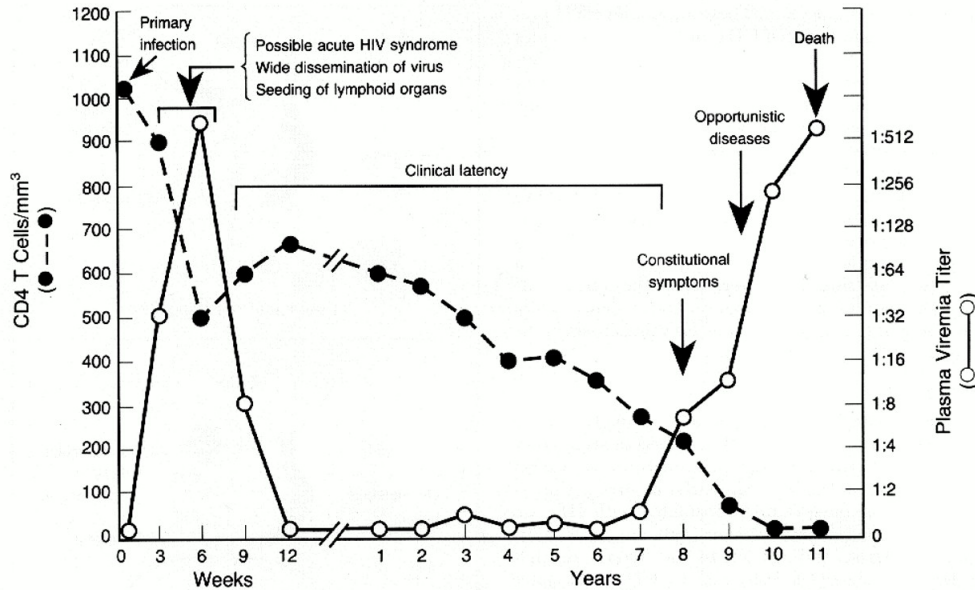


Figure 1.1: The typical course of HIV infection. Adapted from [27]. Plasma viremia titer (i.e., right vertical axis) means the lowest concentration of virus that still infects cells. Titer testing employs serial dilution. In this case, two-fold serial dilution is used. For example, 1:256 indicates that virus infected cells at the first 8 serial two-fold dilutions of plasma.

The asymptomatic stage shows few or no symptoms and can last anywhere from two weeks to twenty years and beyond. The median period of time is approximately 10 years in western countries [27, 32, 33].

The late stage including AIDS shows an increase in viral load and symptoms of various opportunistic infections.

The change in viral load and CD4<sup>+</sup>T cells is shown in Fig. 1.1. In our models of sexual transmission of HIV, neither viral load nor CD4<sup>+</sup>T cells is explicitly modeled. Instead, we model transmission probability per sex act. Transmission probability per sex act is based on recent prospective cohort study of Rakai, Uganda [34] and new interpretations the same data [35, 36]. Per-act transmission probabilities during

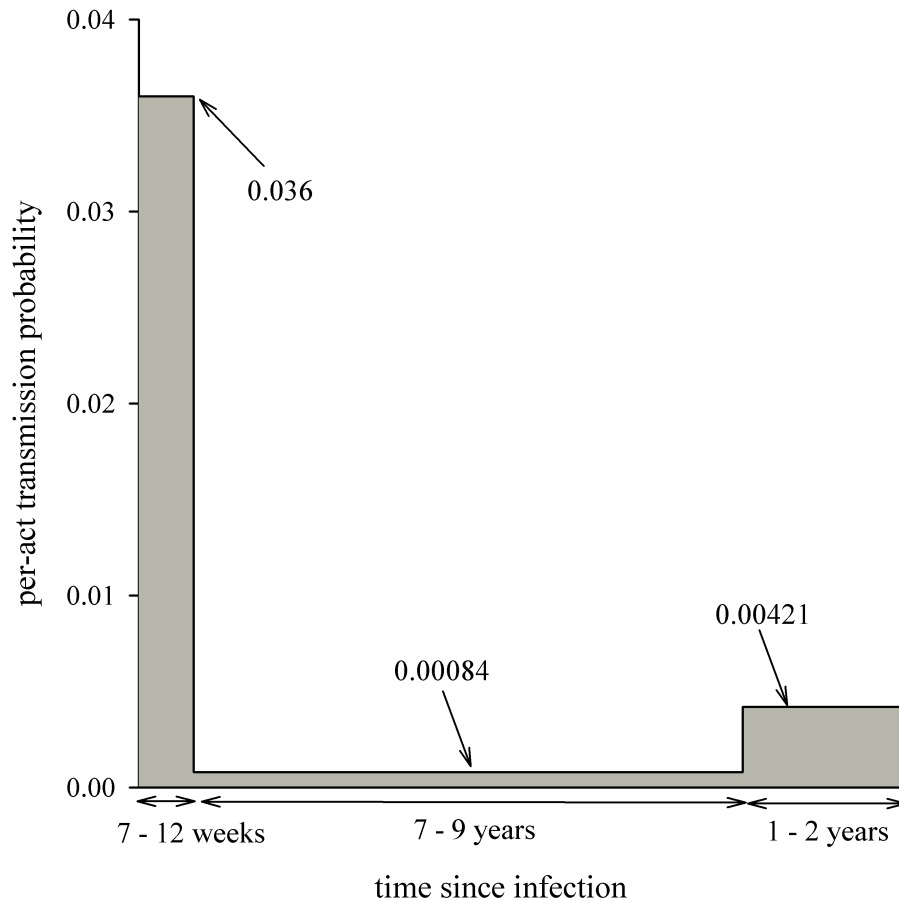


Figure 1.2: Transmission probability per sex act over the course of HIV infection used in our models. Based on [34, 35, 36]

each stage of HIV infection is shown in Fig. 1.2.

The duration of PHI can vary by its definition. For example, in [37], PHI is defined as the time since infection until viral “set point” is established and may last 4-6 months. In this case, PHI includes *acute HIV infection* which describes interval during which HIV can be detected in blood serum and plasma before the formation of antibodies routinely used to diagnose infection [38] and *early HIV infection* during which antibody is detected and yet viral set point has to be established. Our definition of PHI is similar to acute HIV infection.

In Chapters 3 & 4, we also model the course of HIV infection as two stages—PHI

and chronic stage. Here the chronic stage is modeled as a prolonged, low-infectivity period without a late peak in infectivity. This pattern of infectivity can arise among infected individuals receiving treatments such as highly active antiretroviral therapy (HAART), which has been known to reduce infectivity [39] as well as incidence of opportunistic infections and mortality rates [40, 41]

## 1.5 Dissertation overview

Summary for the chapters followed appear in Table 1.1. In Chapter 2 we present an IBM describing sexual transmission of HIV in a one-sex homogeneous population. The course of HIV infection is modeled as three stages and transmission probability per sex act during each stage is modeled as shown in Fig. 1.2. We examine the endemic prevalence of HIV infection and the fraction of transmissions from PHI at endemic phase under variable durations, numbers, and concurrencies of partnerships.

In Chapter 3 we examine similar issues to those in Chapter 2, but use a DCM with a pair approximation technique rather than an IBM. One benefit of using a DCM is that we can bypass extensive simulations required for an IBM. In this chapter, for the sake of simplicity, we assume that HIV infection has two stages-PHI and the chronic stage-and partnerships always form and dissolve randomly. This simplification helps us examine the transmission system analytically while retaining dynamic networks. We derive  $\mathcal{R}_0$  and also numerically integrate the equations to examine endemic prevalence and the fraction of transmissions from PHI at endemic phase.

In Chapter 4 we extend the model presented in Chapter 3. Instead of a one-sex population, we model transmissions in a heterosexual population where insertive and receptive sex acts have different transmission probabilities. Here the term *heterosexual* means that there are two types of sex acts with each having a different

Table 1.1: Summary for the chapters followed

Chapter	Model type	Main outcomes	Conditions varied
2	IBM	Endemic prevalence and the fraction of transmissions from PHI	Duration and concurrency of partnerships
3	DCM	$\mathcal{R}_0$ and the fractional contribution to $\mathcal{R}_0$ of PHI	Duration and average number of partnerships
4	DCM	$\mathcal{R}_0$ and the fractional contribution to $\mathcal{R}_0$ of PHI	Partnership duration and the risk difference between insertive and receptive sex acts
5	IBM	Endemic prevalence and the fraction of transmissions from PHI	Partnership duration and the rate of fluctuation between low and high risk phases
6	N/A	Summary and future study	N/A

transmission probability. Thus, this model is equally applicable to a homosexual male population where people engage in either insertive or receptive anal sex. We examine the endemic prevalence of HIV infection and the fraction of transmissions from PHI at endemic phase under variable numbers and durations of partnerships and also under variable differences in transmission probabilities between insertive and receptive sex acts.

In Chapter 5 we use an IBM again. In Chapters 2 & 3, we found that long-term partnerships can decrease both endemic prevalence of infection and the fraction of transmissions from PHI at endemic phase. In our other study [42], we found that risk behavior change can have the opposite effects. In this chapter, we examine how endemic prevalence and the fraction of transmissions from PHI at endemic phase change when both long-term partnerships and risk behavior change exist.

In Chapter 6, we summarize our findings and discuss future studies that can complement and strengthen our inferences.

## CHAPTER II

# Effects of Sexual Partnerships on HIV Transmissions by Stage

### 2.1 Abstract

**Objective:** To assess the expected effects of partnership duration and concurrency on human immunodeficiency virus (HIV) prevalence and the fraction of transmissions from primary HIV Infection (PHI).

**Methods:** Stochastic individual-based models of HIV transmission in homogeneous populations with dynamic partnerships were constructed with observed relative contagiousness by stage of infection. Endemic prevalence and the fraction of transmissions from PHI were examined across various durations and concurrencies of partnerships while holding the number of sex acts constant.

**Results:** Increasing the concurrency of partnerships always increases endemic prevalence while increasing duration of partnerships always decreases it. The fraction of transmissions from PHI has a U-shaped relationship with partnership duration. It drops with increasing partnership duration in shorter partnerships but rises in longer partnerships. Transmissions from PHI arise more frequently in a partnership where both partners were originally susceptible, but one partner later becomes infected through a concurrent partnership. In a partnership where both partners are originally discordant upon partnership formation, transmissions from PHI are smaller.

Partnership concurrency modifies the relationship between partnership duration and the fraction of transmissions from PHI. The fraction of transmissions from PHI increases in shorter partnerships, but decreases in longer partnerships with increasing partnership concurrency.

**Conclusions:** Endemic prevalence and the fraction of transmissions from PHI are influenced by the duration and the concurrency of partnerships. To make inferences on the role of PHI, partnerships need to be taken into account.

## 2.2 Introduction

Model analyses have resulted in varying estimates for the fractions of transmissions from three stages of human immunodeficiency virus (HIV) infection—primary, asymptomatic and late stages. Earlier studies showed that transmissions occurring during primary HIV infection (PHI) play a disproportionately large role during the initial period of an epidemic [43] and also when HIV is endemic under certain assumptions of population structure [44]. On the other hand, a model fitted to the San Francisco City Clinic Cohort data produced the highest transmission rate during the late stage, resulting more than 90% of transmissions can be attributed to late-stage individuals [45]. A recent modeling study based on HIV epidemics in sub-Saharan Africa concludes that no single stage of HIV infection is dominant over the others: PHI transmissions play an important role during the initial phase of an epidemic where infection is mostly restrained in high-risk population whereas later stages (i.e., asymptomatic and late stages) play a larger role as the epidemic matures [46].

In those studies [43, 44, 45, 46], the authors broke a population down into several subgroups by sexual risk behavior or age to take the population heterogeneity into account. They, however, assumed each individual has an equal chance to transmit

infection to any other individual within or between subgroups. This “well-mixed” assumption does not allow sex acts to occur repeatedly with the same partners. The well-mixed assumption may be justified for a promiscuous population. However, sexual transmission of HIV in a general population is more appropriately described as each individual having repeated sex acts with a finite number of partners.

The purpose of this study is to examine how the transmission of HIV at equilibrium is influenced by more realistic sexual partnership patterns. To those ends, we constructed a discrete individual-based model where individuals form and dissolve partnerships over time. We examined how the endemic prevalence and the fraction of transmissions from PHI at equilibrium are affected by various durations and concurrencies of partnerships. To highlight the effects of sexual partnerships on the transmission of HIV, we modeled a single homogenous population.

This analysis provides insights needed to evaluate other model analyses of HIV control policies and to guide the design of further model analyses. It shows the endemic prevalence and the fraction of transmissions from PHI are strongly influenced by partnership dynamics. Endemic prevalence monotonically increases as concurrency or dissolution probability (at a given average number of partners) of partnerships increases. On the other hand, the fraction of transmissions from PHI has a U-shaped relationship with partnership duration. It drops with increasing partnership duration in shorter partnerships, but rises in longer partnerships. Furthermore, partnership concurrency modifies this relationship. The fraction of transmissions from PHI increases in shorter partnerships, but decreases in longer partnership with increasing partnership concurrency.



## 2.3 Methods

### 2.3.1 The natural history of HIV infection

The natural history of HIV infection is modeled with three periods, each one having a different transmission probability: 1) PHI, a brief period of high transmission probability lasting on average 49 days [47, 48]; 2) the asymptomatic stage, a period of low transmission probability lasting on average 7 years; 3) the late stage, a period of medium transmission probability lasting on average 1 year.

Per-act transmission probabilities during PHI and asymptomatic stages were based on the analysis [36] of the Rakai study [34]. They are 0.03604 and 0.00084 during PHI and the asymptomatic stage, respectively.

As for the per-act transmission probability during late stage, we computed it from the data for the last two follow-up periods of the “late-stage index partner” cohort from the Rakai study [34]. There were total 66 discordant couples and transmissions occurred in 17 couples. Average number of sex acts were 70.7 per couple. From these information, we computed per-act transmission probability during late stage,  $\lambda_3$ , as follows:

$$\lambda_3 = 1 - (1 - N_T/N)^{1/c}, \quad (2.1)$$

where  $N$  is the number of couples (i.e., 66),  $N_T$  is the number of transmission events (i.e., 17), and  $c$  is the average number of sex acts per couple (i.e., 70.7). A recent study [46] used a similar estimate for per-act transmission probabilities during late stage.

This gives the distribution that 38% of transmissions occur during PHI if the frequency of sex acts of an individual does not change over the course of infection and individuals remain sexually active for 25 years. Parameters for the model appear in Table 2.1. We did not include the non-infectious latent period before PHI

Table 2.1: Model Parameters

Symbol	Descriptions
$\lambda_i$	Transmission probability per sex act during stage $i$ for $i = 1, 2, 3$ (1=PHI, 2=asymptomatic stage, 3=late stage).
$\gamma_i$	Per-day probability of progression from stage $i$ to the next for $i = 1, 2, 3$ (1=PHI, 2=asymptomatic stage, 3=late stage).
$\sigma$	Partnership dissolution probability per day.
$c$	Mean frequency of sex acts per partnership per day.
$\theta$	The ratio of partnership formation probabilities comparing a partnership between two individuals of whom at least one is not single to a partnership between two single individuals.
$N_0$	Initial population size.
$\mu$	Probability that an individual becomes sexually inactive per day.
$Q$	Population-averaged number of partners per person.

since sensitivity analyses showed that our inference does not change qualitatively by including the latent period.

### 2.3.2 Compartmental flows for the model analyzed

Fig. 2.1 shows compartmental flows for the model analyzed. Individuals may be in one of four compartments representing four infection categories—susceptible ( $S$ ), PHI ( $P$ ), asymptomatic stage ( $A$ ), and late stage ( $L$ ). Compartments may be further divided by partnership status. For simplicity, however, we present a diagram with-

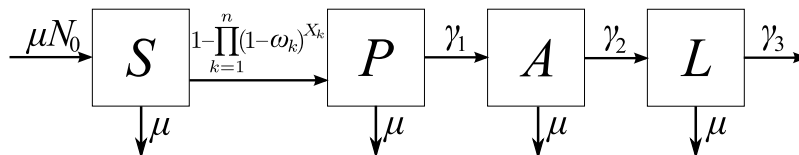


Figure 2.1: Compartmental flow for the model analyzed. The vertical arrows represent removal from the sexually active population. The leftmost horizontal arrow represents susceptible individuals entering the sexually active population. The other horizontal arrows represent infection and stage progression with the final arrow being death from AIDS. See the main text for details.

out partnership status. New susceptible individuals are continuously recruited to the sexually active population in a way that the population size remains constant in the

absence of HIV transmissions. The vertical arrows represent that individuals become sexually inactive. This occurs with the same probability regardless of infection category. The leftmost horizontal arrow represents that new susceptible individuals are recruited to the sexually active population. The other horizontal arrows represent infection and infection progression with the final arrow being death from AIDS.

### 2.3.3 Partnership formation

Partnerships are formed as follows:

1. Two individuals are selected uniformly at random.
2. If two individuals are both single, then they will become partners.
3. If at least one of them is not single, then they will become partners with probability  $\theta$ .
4. Repeat the above procedure until the target number of partnerships has been reached.

Distribution of partnerships across the population can be adjusted using the parameter  $\theta \in [0, 1]$  [49]. This parameter can be interpreted as the ratio of partnership formation probabilities comparing a partnership between two individuals of whom at least one is not single to a partnership between two single individuals. If  $\theta = 1$ , the current partnership status of an individual does not affect the probability of gaining a new partner. Also, since partnership dissolution probability is not influenced by the number of partners an individual has, the number of partners per person follows a Poisson distribution when  $\theta = 1$  in the limit of large population size. If  $\theta = 0$ , no individual may have more than one partner. In short,  $\theta$  provides a transition from overall monogamy to random partnerships where the number of partners per person follows a Poisson distribution.

#### 2.3.4 Partnership dissolution

Partnership dissolution occurs at a probability  $\sigma$  per day regardless of infection category. However, there are two other ways in which partnerships can dissolve; when one's partner dies of AIDS or the partner becomes sexually inactive (i.e., removed from the population at risk). Without deaths from AIDS, average partnership duration in terms of days is roughly  $1/(\sigma + 2\mu)$ , where  $\mu$  indicates the probability that an individual becomes sexually inactive. Since there are two individuals in a partnership, we need  $2\mu$  to calculate partnership duration.

#### 2.3.5 Probability of infection

If a susceptible individual has  $n$  infected partners on a certain day, then the probability that the susceptible individual becomes infected on that day is

$$1 - \prod_{k=1}^n (1 - \omega_k)^{X_k}, \quad (2.2)$$

where  $\omega_k$  is the transmission probability per sex act for the  $k$ th infected partner, which is determined by the infected partner's stage of infection (i.e.,  $\omega_k = \lambda_1, \lambda_2, \lambda_3$ ).  $X_k$  is the frequency of sex acts per day in the partnership between the susceptible and the  $k$ th infected partner. This is a Poisson random variable with parameter  $c$ , which is the mean frequency of sex acts per partnership per day.

#### 2.3.6 Model simulation

We start off with an entirely susceptible population of the initial size  $N_0$ . Partnerships are formed until the number of partnerships reaches the target number,  $0.5QN_0$ , where  $Q$  is the target average number of partners per person. Once partnerships are generated, we randomly choose 0.1% of the population and set them as the initially infected individuals who have PHI. Total run time was 100,000 time

steps, with each step corresponding to one day. Population size decreases as death from AIDS occurs. After infection dynamics have come to equilibrium, variables of interest were measured. For example, endemic prevalence was first calculated as an average over the last 40,000 time steps for each simulation run. Then, an average and a standard deviation were calculated from 10 simulation runs.

The following events occur at each time step:

1. New partnerships are formed until the number of partnerships in the population reaches the target number,  $0.5QN_t$ . Here  $N_t$  is population size at current time step.
2. Transmission occurs in a partnership of a susceptible and an infected individuals.
3. Infected individuals progress from stage  $i$  to the next with probability  $\gamma_i$  for  $i = 1, 2$  (1=PHI, 2=asymptomatic stage).
4. Late-stage individuals die (i.e., are removed) with probability  $\gamma_3$ . Partnerships involving dying individuals dissolve.
5. Individuals are removed from the sexually active population with probability  $\mu$ . Partnerships involving removed individuals dissolve.
6. Partnerships dissolve with probability  $\sigma$ .
7. A new susceptible is recruited with probability  $\mu$ , which is repeated for  $N_0$  times.

## 2.4 Results

We examine the endemic prevalence and the fraction of transmissions from PHI in a homogenous population as we vary partnership duration and average number of partners per person.

### 2.4.1 Partnership duration varies while average number of partners does not

In this case, we keep the average number of partners per person constant as partnership duration is varied. Since the average number of partners per person does not change, when the number of sex acts per partnership per day is kept constant, the expected number of sex acts per person per day is also kept constant.

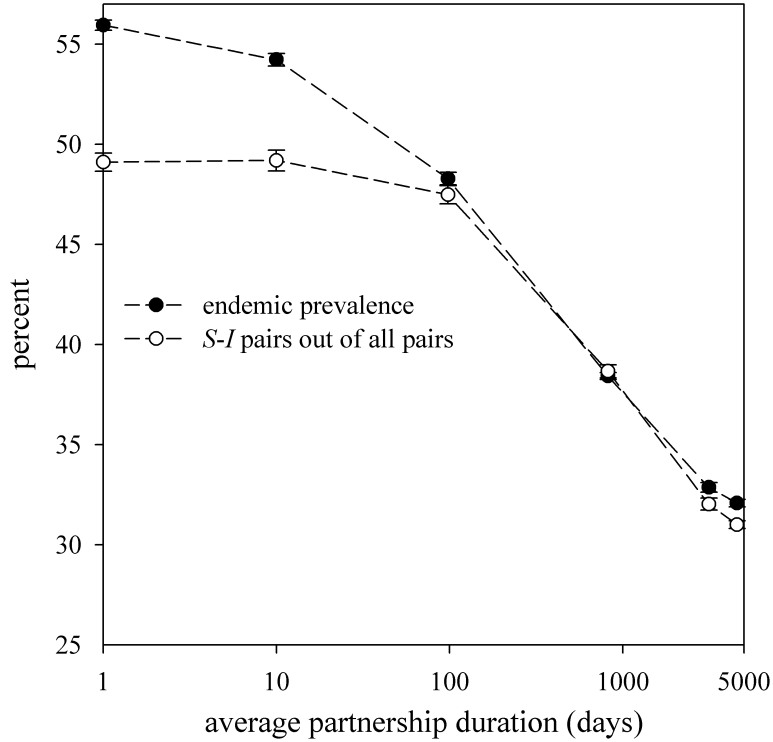


Figure 2.2: Endemic prevalence and the fraction of  $S-I$  pairs out of total pairs across partnership duration.  $Q = 1.5, c = 0.3333, \lambda_1 = 0.03604, \lambda_2 = 0.00084, \lambda_3 = 0.0042, \gamma_1 = 1/49, \gamma_2 = 1/2555, \gamma_3 = 1/365, \mu = 1/9125, \theta = 1$ , and  $N_0 = 10000$ . Average partnership duration is calculated as  $1/(2\mu + \sigma)$ . Each data point is the mean from ten simulation runs and error bars indicate one standard deviation.

As seen in Fig. 2.2, endemic prevalence of HIV infection monotonically decreases with increasing partnership duration. The decrease in endemic prevalence with increasing partnership duration arises because in prolonged partnerships, once transmission occurs, infected individuals have sex with someone they have already infected. That is, fewer sex acts of infected individuals are with susceptible individ-

uals. By contrast, in shorter partnerships, infected individuals are freed from their infectors or their infectees more quickly and meet new partners more often so they have a higher chance of having sex with susceptible individuals. Since transmissions occur only in discordant pairs (labeled  $S-I$  pairs), the decrease in endemic prevalence is associated with the decrease in discordant pairs out of total pairs, as is also seen in Fig. 2.2.

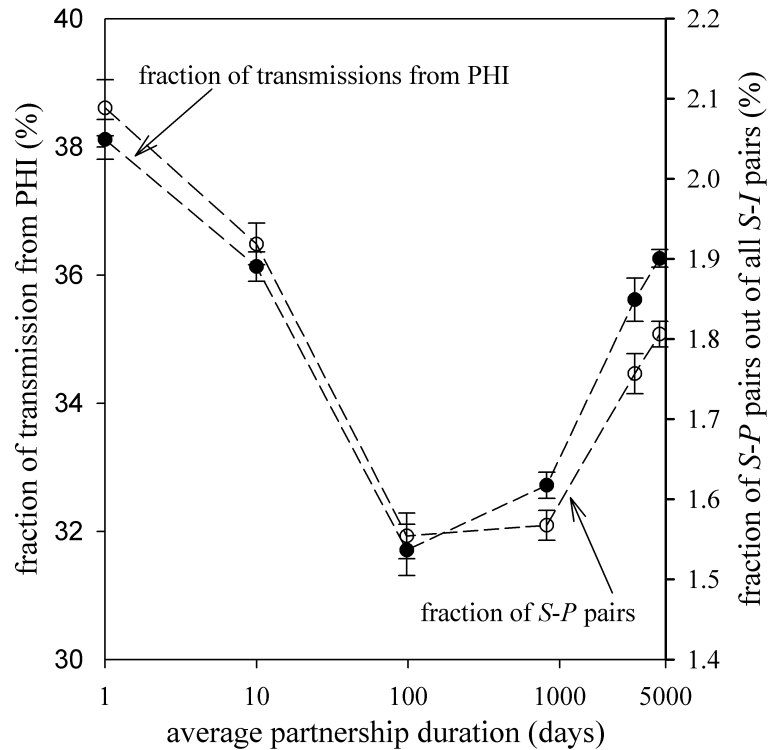


Figure 2.3: Fraction of transmissions from PHI and the fraction of  $S-P$  pairs out of all  $S-I$  pairs across partnership duration. An  $S-I$  pair denotes a pair between a susceptible and an infected and an  $S-P$  pair denotes a pair between a susceptible and an infected with PHI. Parameter values are the same as in Fig. 2.2

In contrast to the monotonic decrease in prevalence, the fraction of transmissions from PHI first falls and then rises, as seen in Fig. 2.3. This pattern is directly related to the fraction of discordant pairs where the infected individual has PHI (labeled  $S-P$  pairs).

As Fig. 2.4 illustrates, the fraction of  $S$ - $P$  pairs has different patterns for pairs that are discordant upon partnership formation (in short, originally discordant  $S$ - $I$  pairs) and those that are originally concordantly susceptible where one individual becomes infected through a concurrent partnership (in short,  $S$ - $I$  pairs that were originally concordantly susceptible).

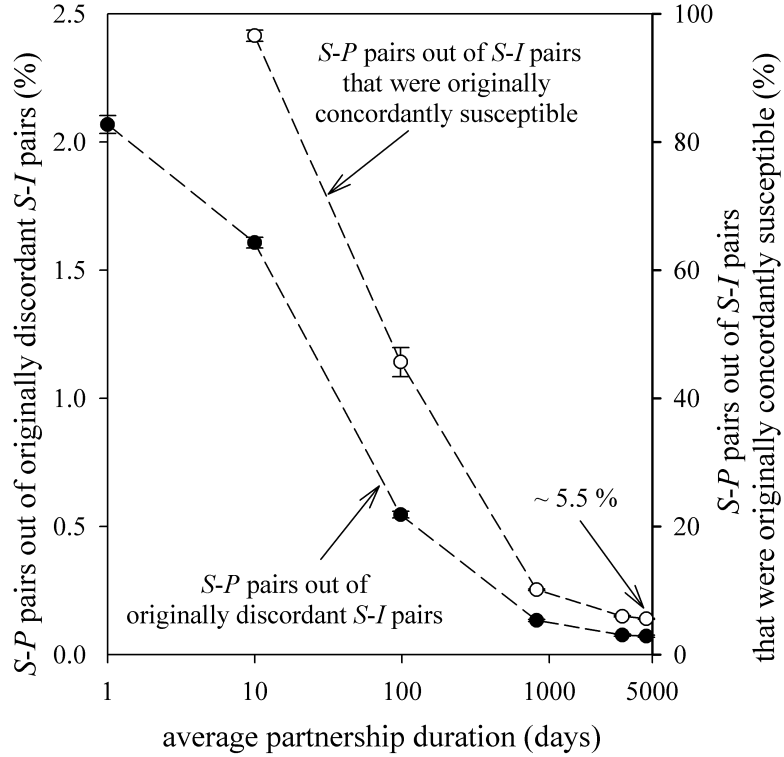


Figure 2.4: Fraction of  $S$ - $P$  pairs out of originally discordant  $S$ - $I$  pairs and out of  $S$ - $I$  pairs that were originally concordantly susceptible across partnership duration. The open circles are not present at the leftmost points because there are no  $S$ - $I$  pairs that were originally susceptible when every partnership dissolves at each time step. Parameter values are the same as in Fig. 2.2.

To understand the pattern of the fraction of  $S$ - $P$  pairs across partnership duration, consider first the fraction of  $S$ - $P$  pairs out of originally discordant  $S$ - $I$  pairs. When every partnership changes at each time step (i.e., leftmost points in Fig. 2.4), the fraction of  $S$ - $P$  pairs is approximately 2.1%. This fraction equals the equilibrium fraction of infecteds who have PHI out of all infecteds (based on parameter values



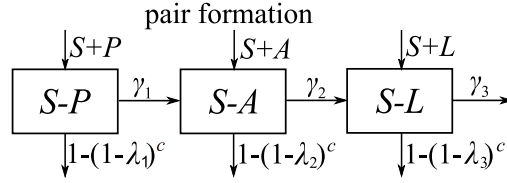
of our model). This is natural since susceptibles form partnerships with infecteds independent of infection stages.

To understand why this fraction decreases with increasing partnership duration, see the top diagram in Fig. 2.5. In the diagram two flows are most likely to affect the fraction of  $S-P$  pairs.

First, outflows by transmission (i.e., downward arrows) in ongoing partnerships are relatively larger for  $S-P$  pairs than  $S-A$  or  $S-L$  pairs because of higher transmission probability during PHI. As seen in Fig. 2.6, the fraction of  $S-P$  pairs in ongoing partnerships decreases because of higher transmission rate during PHI as average partnership duration (i.e., time elapsed after pair formation) increases. Second, the outflow from  $S-P$  pairs via progression (i.e., the rightward arrow) becomes an additional inflow to  $S-A$  pairs in ongoing partnerships. Accordingly, the fraction of  $S-P$  pairs out of originally discordant  $S-I$  pairs decreases with increasing partnership duration.

Next, consider the fraction of  $S-P$  pairs out of  $S-I$  pairs that were originally concordantly susceptible. As seen in Fig. 2.4, this fraction is high in shorter partnerships. This is because inflows to  $S-A$  and  $S-L$  pairs are solely from stage progression of  $S-P$  pairs (see the bottom diagram in Fig. 2.5). That is, if partnership duration is not long enough for individuals who have PHI to progress to asymptomatic and then to late stages or if susceptible partners are infected during the partner's PHI, there will be no  $S-A$  or  $S-L$  pairs. The fraction of  $S-P$  pairs decreases with increasing partnership duration, but it always remains much higher than the fraction of  $S-P$  pairs in originally discordant  $S-I$  pairs. Note that the lowest fraction of  $S-P$  pairs out of  $S-I$  pairs that were originally concordantly susceptible is about 5.5% whereas the lowest fraction of  $S-P$  pairs out of originally discordant  $S-I$  pairs is about 2.1%.

1. originally discordant  $S-I$  pairs



2.  $S-I$  pairs that were originally concordantly susceptible

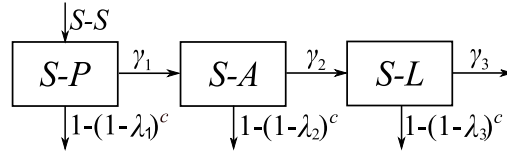


Figure 2.5: Compartmental flows among discordant pairs.  $i-j$  indicates a pair between one individual in state  $i$  and the other in state  $j$  for  $i, j = S, P, A, L$ .  $i + j$  indicates pair formations between individuals in states  $i$  and  $j$ .  $S-S \rightarrow S-P$  indicates infection of a susceptible in a pair between two susceptibles through a concurrent partnership.  $c$ ,  $\lambda_i$  and  $\gamma_i$  for  $i = 1, 2, 3$  denote mean number of sex acts per partnership per day, transmission probability per act and stage progression probability per day, respectively.

The fraction of  $S-P$  pairs out of total  $S-I$  pairs is determined by fractions of these two types of  $S-I$  pairs and the fraction of  $S-P$  pairs out of each type. Fig. 2.7 shows the fractions of two types of  $S-I$  pairs across partnership duration. In shorter partnerships (e.g.,  $< 1000$  days), almost all of  $S-I$  pairs are originally discordant. Since the fraction of  $S-P$  pairs decreases fast with increasing partnership duration in this type of  $S-I$  pairs, the fraction of  $S-P$  pairs out of total pairs decreases with increasing partnership duration. In longer partnerships, the decrease in the fraction of  $S-P$  pairs in both types of  $S-I$  pairs slows, as shown in Fig. 2.4. On the other hand, as seen in Fig. 2.7, the fraction of  $S-I$  pairs that were originally concordantly susceptible, where the fraction of  $S-P$  pairs is high, increases fast in longer partnerships. Accordingly, the fraction of  $S-P$  pairs out of total  $S-I$  pairs increases again in longer partnerships. Therefore, the fraction of  $S-P$  pairs and thus the fraction of transmissions from PHI have a U-shaped relationship with partnership duration, as

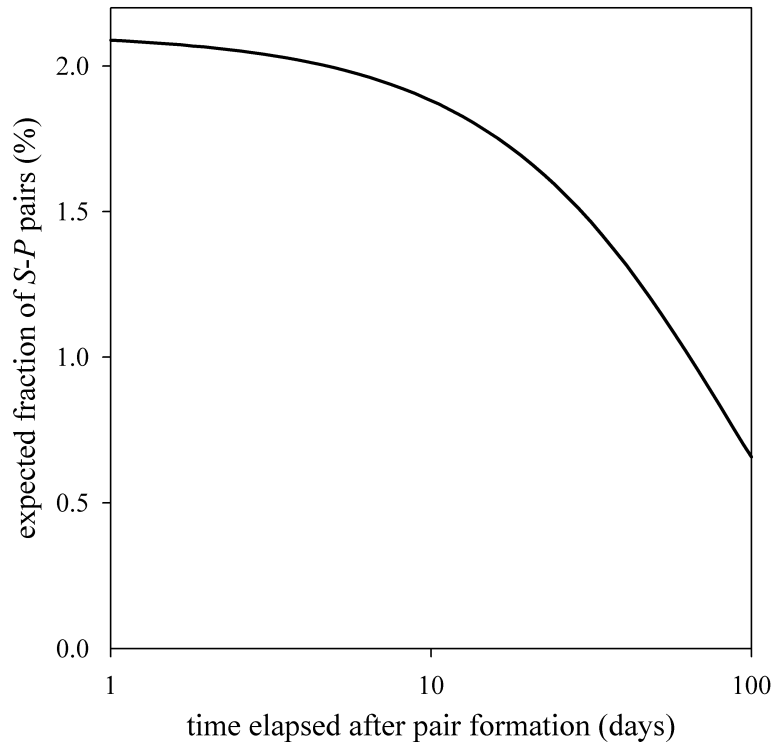


Figure 2.6: Expected fraction of  $S$ - $P$  pairs as a function of time elapsed after pair formation. We assume that the numbers of pairs change only through transmission. The initial fraction of  $S$ - $P$  pairs (2.1%) was chosen based on the fraction of infecteds who have PHI out of all infecteds at equilibrium if partnerships dissolve at each time step. The number of sex acts per day per partnership,  $c$ , is 0.3333

shown in Fig. 2.3

#### 2.4.2 Average number of partners as well as partnership duration is varied.

In this and the next analyses, we examine the effects of partnership concurrency. Our measure of partnership concurrency is proportional to the fraction of individuals who have multiple partners. In this first analysis, partnership concurrency is increased by increasing the population-averaged number of partners per person. As the average number of partners is varied, the sex act rate per partnership is also varied to keep the total rate of sex acts the same across the population. Partnership concurrency can also be varied while keeping the population-averaged number of partners constant by changing the distribution of partnerships across individuals.

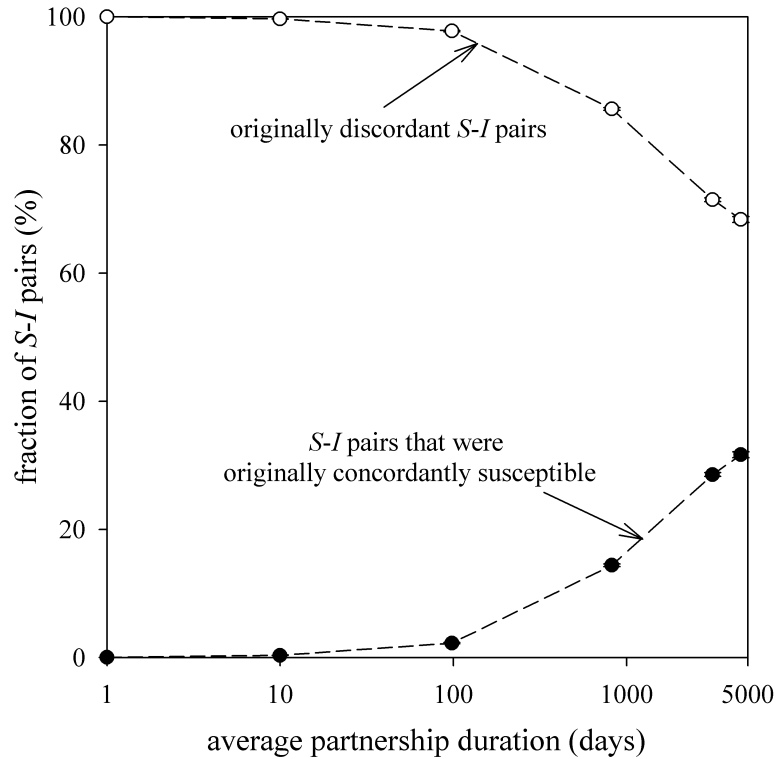


Figure 2.7: Fraction of  $S-I$  pairs that were originally discordant or that were originally concordantly susceptible out of total  $S-I$  pairs. Parameter values are the same as in Fig. 2.2.

This is examined in the next section. In this section we assume that the number of partners follows a Poisson distribution.

As seen in Fig. 2.8, the endemic prevalence is higher for higher average number of partners at a given partnership duration and decreases with increasing partnership duration. The increase in endemic prevalence with increasing average number of partners is because of the decrease in the number of sex acts per partnership. Slower transmission in a partnership means that fewer sex acts are between already infected partners and more sex acts are between susceptible and infected individuals. Therefore, fewer sex acts are “wasted” and so the endemic prevalence is higher when average number partners is higher (i.e., transmission rate per partnership is lower).

As seen in Fig. 2.9, the general pattern of the fraction of transmissions from PHI—

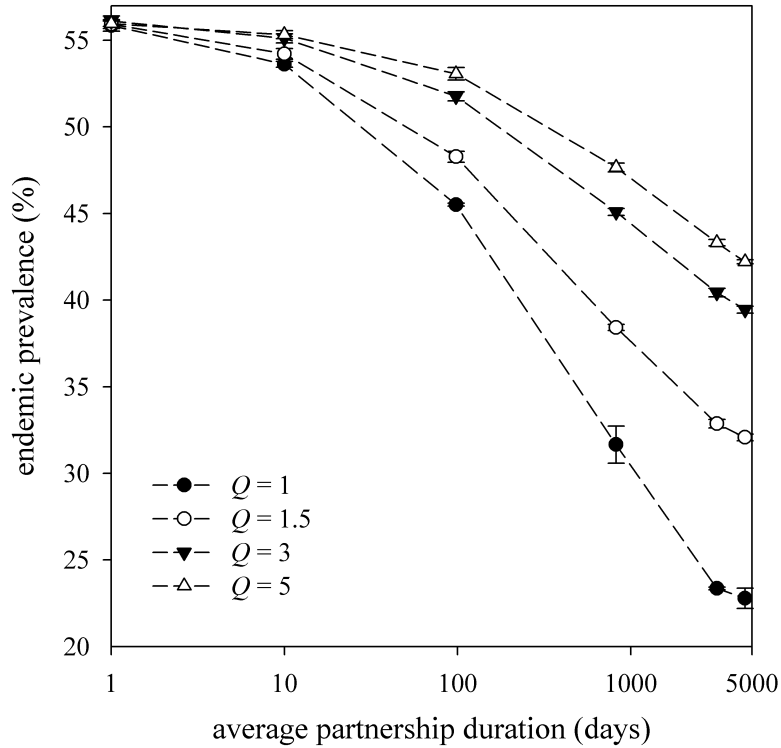


Figure 2.8: Endemic prevalence across partnership duration at four levels of  $Q$ . The product of the number of sex acts per partnership per day,  $c$ , and  $Q$  remains constant at 0.5. All the other parameter values are the same as in Fig. 2.2

an initial decrease followed by a later increase—is similar for all levels of average number of partners. A new phenomenon, however, emerges in this analysis. As the concurrency number increases, the rate of fall of the fraction of transmissions from PHI with increasing partnership duration is decreased and the inflection point where that fraction begins to rise again is pushed to longer partnership durations with a slower subsequent rise. The highest fraction of transmissions from PHI is seen when the concurrency number is low and thus the sex act rate per partnership is high given very long partnerships.

As seen in Fig. 2.10, the fraction of  $S$ - $P$  pairs of total  $S$ - $I$  pairs is directly associated with the fraction of transmissions from PHI. The fraction is higher for higher average number of partners in shorter partnerships (e.g.,  $\leq 1000$  days), but it has the

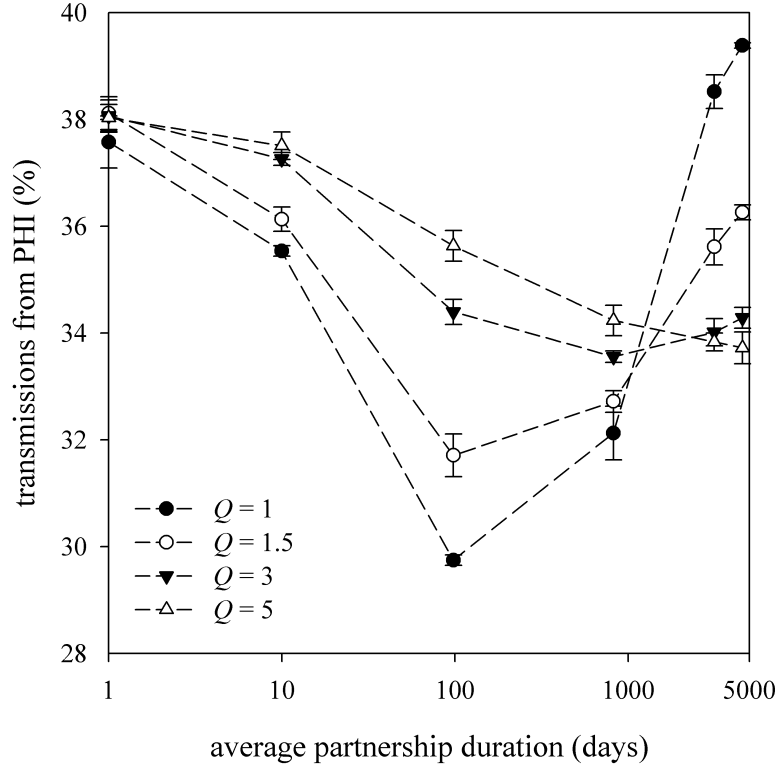


Figure 2.9: Fraction of transmissions from PHI across partnership duration at four levels of average number of partners,  $Q$ . The product of the number of sex acts per partnership per day,  $c$ , and  $Q$  remains constant at 0.5. Parameter values are the same as in Fig. 2.2

opposite pattern in longer partnerships (e.g.,  $> 1000$  days). The general pattern—an initial decrease followed by a later increase—is similar at all levels of average number of partners.

As mentioned earlier, as average number of partners is increased, the frequency of sex acts per partnership is decreased. Also, higher average number of partners means higher partnership formation probability at a given partnership duration. These two differences differentially affect  $S-P$ ,  $S-A$ , and  $S-L$  pairs and generate pattern seen in Figs. 2.9 and 2.10.

For example, the decreased frequency of sex acts per partnership with increasing concurrency number reduces the relative difference in transmission rate per partnership across different types of  $S-I$  pairs. As seen in Fig. 2.11, this causes the fraction

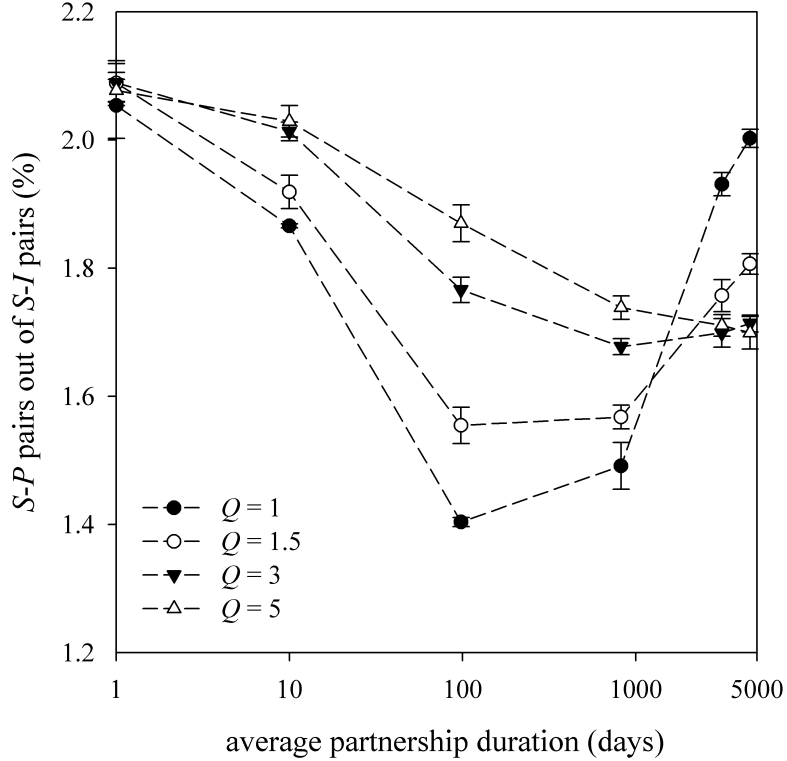


Figure 2.10: Fraction of  $S-P$  pairs out of total  $S-I$  pairs across partnership duration at four levels of average number of partners,  $Q$ . Parameter values are the same as in Fig. 2.2

of  $S-P$  pairs to be higher for higher concurrency in shorter partnerships (i.e., relatively reduced outflow from  $S-P$  in Fig. 2.5 compared with  $S-A$  or  $S-L$ ). Thus, the fraction  $S-P$  pairs and the fraction of transmissions from PHI is higher for higher average number of partners in shorter partnerships.

#### 2.4.3 Partnership concurrency at a given average number of partners as well as partnership duration is varied

In this case we vary the partnership concurrency from monogamy at one extreme to Poisson distribution of the previous section at the other extreme while keeping the average number of partners constant. Since the maximum average number of partners per person is one in monogamy, we set average number of partners at 0.9. Fig. 2.12 shows the distribution of number of partners per person across  $\theta$ . If  $\theta = 0$ , then there are only two groups of individuals: single individuals and those who have

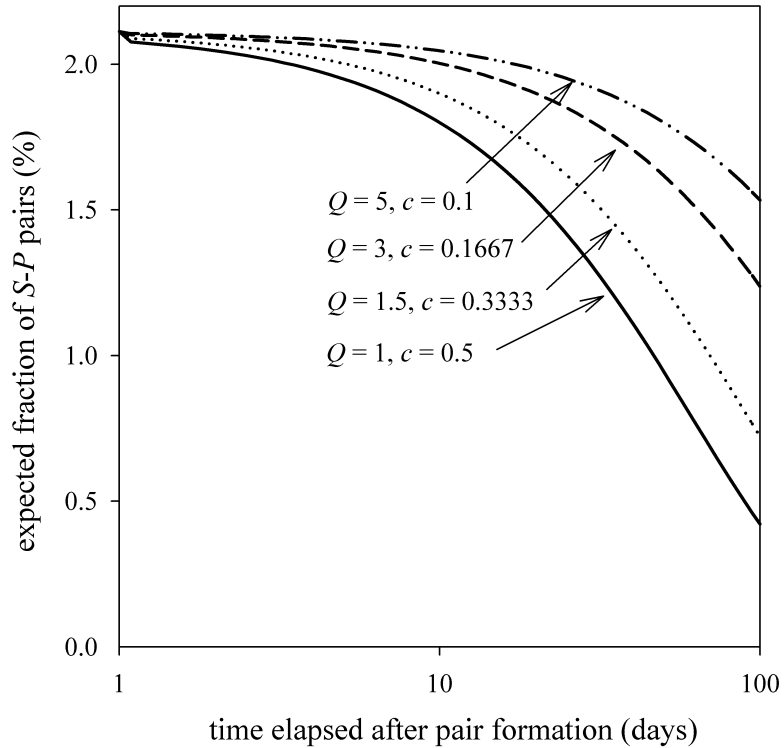


Figure 2.11: Expected fraction of  $S$ - $P$  pairs as a function of time elapsed after pair formation at four levels of average number of partners,  $Q$ . We assume that the numbers of pairs change only through transmission. The initial fraction of  $S$ - $P$  pairs (2.1%) was chosen based on the fraction of infecteds who have PHI out of all infecteds at equilibrium if partnerships dissolve at each time step. The product of  $Q$  and the number of sex acts per day per partnership,  $c$ , remains constant at 0.5.

one partner. As  $\theta$  is increased from 0 to 1, the fraction of individuals who have more than one partner (i.e., degree  $\geq 2$ ) increases. For this reason, we assume partnership concurrency increases with increasing  $\theta$  although the population-averaged number of partners remains constant.

As seen in Fig. 2.13, the endemic prevalence is higher for higher  $\theta$  at a given partnership duration and decreases with increasing partnership duration. This has previously been described by other researchers. The main reason is the increase in the number of individuals connected in the network at any point in time (i.e., the size of the largest component) [50].

As seen in Fig. 2.14, fraction of transmissions from PHI is higher for higher  $\theta$



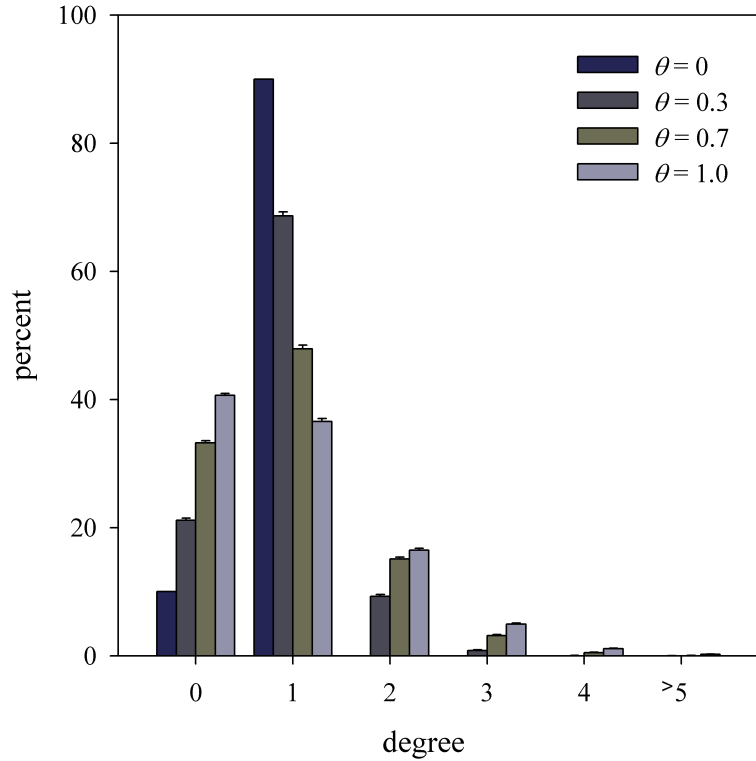


Figure 2.12: Degree distribution at four levels of  $\theta$ . Average number of partners per person,  $Q$ , is 0.9. “Degree” of an individual means the number of partners the individual has. Each bar represents an average from ten simulation runs and the error bar shows one standard deviation.

in shorter partnerships (e.g.,  $\leq 1000$  days) whereas it has the opposite pattern in longer partnerships. The general pattern—an initial decrease followed by a later increase—is similar for all levels of  $\theta$ . The lines are truncated for  $\theta = 0, 0.3$  because infection dies out if partnership duration is longer than 1000 days.

As seen in Fig. 2.15, the fraction of  $S$ - $P$  pairs of total  $S$ - $I$  pairs is directly associated with the fraction of transmissions from PHI. The fraction is higher for higher  $\theta$  in shorter partnerships (e.g.,  $\leq 1000$  days) and it has the opposite pattern in longer partnerships (e.g.,  $> 1000$  days). The general pattern—an initial decrease followed by a later increase—is similar at all levels of  $\theta$ .

Unlike the average number of partners,  $\theta$  does not influence the frequency of sex acts per partnership. Instead, lower  $\theta$  means lower partnership formation probability

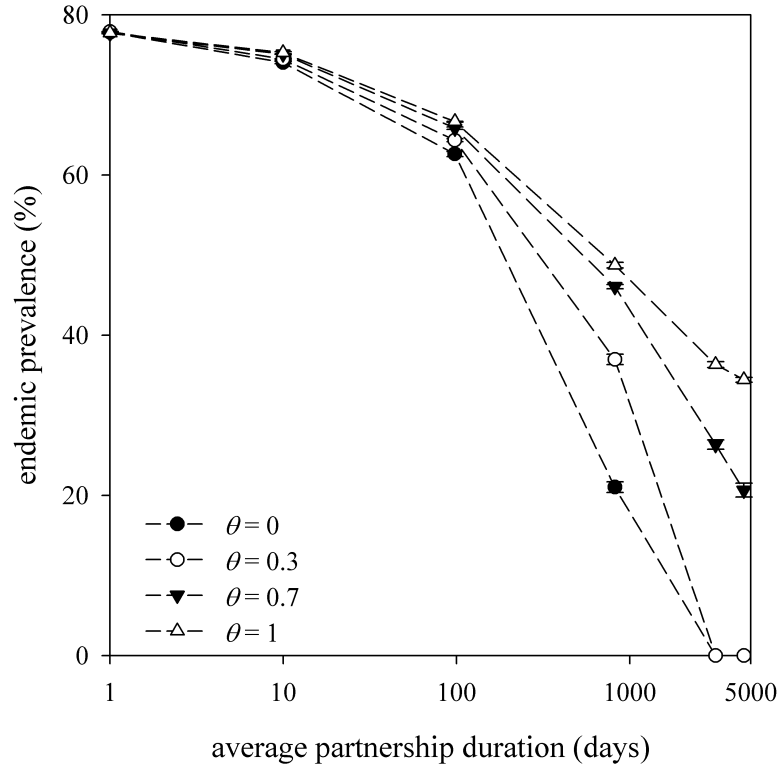


Figure 2.13: Endemic prevalence across partnership duration at four levels of  $\theta$ . Average number of partners per person,  $Q$ , is 0.9. The number of sex acts per day per partnership,  $c$ , is 1.1111. All the other parameter values are the same as in Fig. 2.2

for individuals with a partner. This differentially affects  $S$ - $P$ ,  $S$ - $A$ , and  $S$ - $L$  pairs and generates pattern seen in Figs. 2.14 and 2.15.

For example, at lower  $\theta$ , individuals with PHI have a lower partnership formation probability than later-stage individuals because individuals with PHI are more likely to remain connected to their infectors. That is, decreasing  $\theta$  reduces inflow to  $S$ - $P$  in Fig. 2.5 (upper diagram). Accordingly, the fraction of  $S$ - $P$  pairs and the fraction of transmissions from PHI are lower for lower  $\theta$  in shorter partnerships.

## 2.5 Discussion

Relative infectiousness during different stages of HIV infection is one important factor determining the fraction of transmissions during PHI. The empirical data from

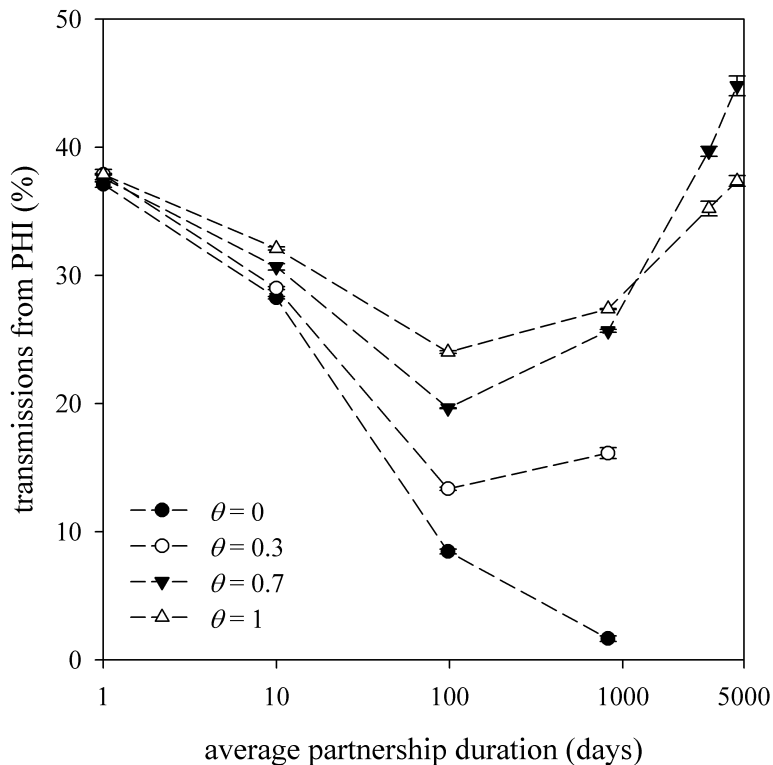


Figure 2.14: Fraction of transmissions from PHI (%) across partnership duration at four levels of  $\theta$ . Average number of partners per person,  $Q$ , is 0.9. The number of sex acts per day per partnership,  $c$ , is 1.1111. All the other parameter values are the same as in Fig. 2.2

Rakai study [34] and new interpretations of the data [35, 36] ignore other factors which we show here to affect that fraction. These are the duration and concurrency of sexual partnerships across the population. Within realistic parameter ranges for partnership duration in populations that are sustaining HIV transmission, the homogeneous population model we examined generated a lower fraction of transmissions during PHI when partnerships last for a few months to a few years than when all partnerships are instantaneous or last more than a decade. Thus realistic violation of the intrinsic assumption of instantaneous partnerships in differential equation models of HIV transmission like those of [44, 45, 46] could potentially be overestimating transmissions arising from early infections.

It is important that models assessing the effects of control programs get the role

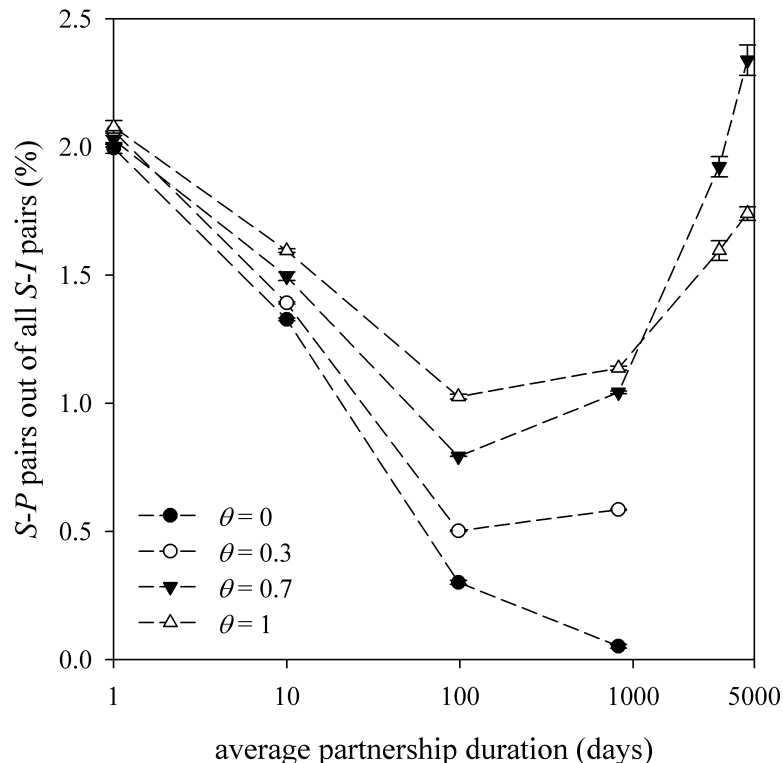


Figure 2.15: Fraction of  $S-P$  pairs out of total  $S-I$  pairs across partnership duration at four levels of  $\theta$ . Average number of partners per person,  $Q$ , is 0.9. The number of sex acts per day per partnership,  $c$ , is 1.1111. All the other parameter values are the same as in Fig. 2.2

of PHI transmissions right since the numerous programs that depend upon identifying HIV-positive individuals and slowing transmission from them are likely to have little or no effect on transmissions that occur during PHI. If PHI transmissions are important, such control programs could have little effects.

The studies by Kretzschmar and colleagues are particularly relevant to our study [51, 52]. Their studies indicate that the role of PHI decreases in long-term partnerships, which is, in part, consistent with our inferences. Our model analyses, however, show that the fraction of transmissions from PHI increases again after an initial decrease as partnership duration increases.

Our results should not lessen concern about this issue nor decrease the focus on controlling transmission during PHI. We examined the simplest possible individual-

based model of HIV transmission through dynamic partnerships in order to elucidate mechanisms through which partnerships affect transmission dynamics and PHI transmissions. In this simple model we can see clearly that transmission in new partnerships made with infected individuals and transmission in standing partnerships where a partner becomes newly infected through a concurrent partnership are quite different. In standing partnerships, the fraction of transmissions from PHI is considerably higher than that from post-PHI.

One of the important conclusions from our analysis is that realistic assessment of potential interventions with transmission system model analyses must employ models that capture the effects of ongoing but dynamic partnerships. A crucial issue is finding data to validate such models. Direct data on partnership duration and concurrency [53, 54, 55, 56, 57] will be valuable. Analyses of more realistic partnership models will be needed, however, to define what new data collection of this sort should be pursued. We believe that a useful source of data will be nucleotide sequence data like that presented in Brenner *et al.* [58]. We believe that models of dynamic partnerships in which PHI plays different roles will generate different transmission tree patterns that can be perceived through such analyses.

## CHAPTER III

# Effects of Sexual Partnership Dynamics on HIV Transmissions by Stage

### 3.1 Abstract

**Objective:** We sought to understand how dynamics of sexual partnerships affect transmissions of human immunodeficiency virus (HIV) during primary HIV infection (PHI) and chronic stage.

**Methods:** Using ordinary differential equations, we constructed models of HIV transmission in a homogeneous population where sexual partnerships are formed and broken. We use two models. In one model, the infectious period is represented by a single compartment (i.e., the  $SI$  model) and in the other, it is divided into two compartments (i.e., the  $SI_1I_2$  model) across which infectivities vary. For these two models, we derive the basic reproductive ratio,  $\mathcal{R}_0$ , and numerically integrate the equations to evaluate endemic prevalence and the fraction of transmissions from PHI at endemic phase.

**Results:** In both  $SI$  and  $SI_1I_2$  models,  $\mathcal{R}_0$  monotonically increases with increasing average number of partners and with decreasing partnership duration.  $\mathcal{R}_0$  is expressed as a function of not just a transmission potential, the product between the duration of infection and the transmission rate, but also a correlation between susceptible and infected individuals. In particular, if partnerships have a finite duration,

the correlation becomes smaller with increasing transmission rate. This means  $\mathcal{R}_0$  is larger for a lower transmission rate with a longer duration of infection at a given transmission potential. In instantaneous or fixed partnerships,  $\mathcal{R}_0$  is not affected by varying transmission rate or the duration of infection at a given transmission potential. In the  $SI_1I_2$  model, the fractional contribution to  $\mathcal{R}_0$  of PHI and the fraction of transmissions from PHI at endemic phase have a U-shaped relationship with partnership duration. They drop in shorter partnerships with increasing partnership duration, but rise in longer partnerships. These patterns are explained by the change in the correlation between susceptible and infected individuals, which indicates the fraction of susceptible partners of infected individuals relative to the population average. The change in the fraction of susceptible partners is, in turn, explained by the interaction between variable infectivity across the stage of infection, stage progression, and partnership duration.

**Conclusions:** The transmission of HIV is influenced by partnership dynamics. Models comparing the roles of different stages of HIV infection need to take partnership dynamics into account.

### 3.2 Introduction

Infection with human immunodeficiency virus (HIV) is marked with a variable infectivity over the course of infection. Along with previous studies [47, 48], a recent study of Ugandan population [34] and new analyses of the same data [35, 36] provide estimates for the duration and per-act transmission probability for three stages of HIV infection—primary, asymptomatic and late stages.

These estimates are useful for understanding characteristics of HIV transmission. For example, under some simplifying assumptions, we can compute how many sec-

ondary cases an index case will produce on average. If the index case always meets new susceptible people during its entire course of infection, the average number of secondary cases is called the basic reproductive ratio,  $\mathcal{R}_0$ . It can be expressed as the product of the duration of infection, the per-act transmission probability, and the sex act rate per unit time. We can also compute what proportion of new infections are attributable to a particular stage of infection. For example, the fraction of new infections attributable to primary HIV infection (PHI) at equilibrium will be the transmission potential during PHI out of transmission potential over the entire course of infection given that the infected individual meets susceptibles randomly regardless of the stage of infection. Here the transmission potential means the product of the duration of infection and per-act transmission probability at a given sex act rate.

In reality, however, assumptions underlying those simple computations are not usually met. For example, one common assumption states that individuals are “well-mixed.” That is, every individual is assumed to have an equal chance to meet and infect any other individual in the population. This assumption is not realistic, especially for sexual transmission of HIV, because an infected individual can only infect his or her sex partners, which is likely to be a small subset of any given population.

The well-mixed assumption is relaxed in so-called network models [11, 15, 16, 59] where nodes and edges represent individuals and sexual partnerships between them, respectively. One conclusion from those studies is that an epidemic quantity such as  $\mathcal{R}_0$  is not just a function of duration of infection and transmission probability but also is related to parameters defining dynamics or configuration of the underlying network. It follows then the fraction of transmissions from a particular stage of



infection in the network model will also be related to underlying networks.

Estimating correct  $\mathcal{R}_0$  is important to understanding infection transmission [18].  $\mathcal{R}_0$  tells about the epidemic threshold: if  $\mathcal{R}_0 < 1$ , an epidemic dies out and otherwise a significant fraction of the population will be infected. Therefore, under some simplifying assumptions, it shows how much we need to reduce infectivity or shorten the duration of infection to stop the epidemic. Likewise, getting correct estimates for the fraction of transmissions from a particular stage of HIV infection is important. This is because effectiveness of certain HIV control programs will depend on how many transmissions arise during a particular stage. For example, an HIV vaccine that may not prevent infection, but still lowers the initial peak of virus level [60, 61] or treating infecteds who have already passed their PHI will have a different effectiveness depending on the proportion of transmissions during different stages of HIV infection.

In this paper we examine how  $\mathcal{R}_0$  in HIV transmission and the contribution to  $\mathcal{R}_0$  of PHI is influenced by dynamic sexual partnerships. Using ordinary differential equations, we constructed a model of HIV transmission in a homogeneous population with dynamic partnerships. We derive  $\mathcal{R}_0$  and illustrate how the fractional contribution to  $\mathcal{R}_0$  of PHI are influenced by the number and the duration of partnerships. We also numerically integrate the equations to examine endemic prevalence and the fraction of transmissions from PHI at endemic phase.

$\mathcal{R}_0$  and the fractional contribution to  $\mathcal{R}_0$  of PHI are strongly influenced by the duration and the number of partnerships. With increasing partnership duration,  $\mathcal{R}_0$  decreases monotonically whereas the fractional contribution to  $\mathcal{R}_0$  of PHI initially decreases and then increases again. This pattern is modified by the number of partners. Similar patterns are observed for endemic prevalence and the fraction of

transmissions from PHI at endemic phase. These patterns are explained by the difference in the fraction of susceptible partners by stage of HIV infection. This is, in turn, explained by the interaction among variable infectivity over the course of infection, stage progression, and partnership duration.

### 3.3 Methods

#### 3.3.1 Compartmental flows for the model analyzed.

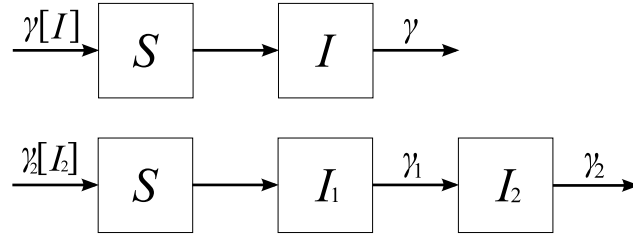


Figure 3.1: Compartmental flows for the model analyzed. An arrow from  $S$  to  $I$  (upper diagram) or to  $I_1$  (lower diagram) indicates infection transmission. Population size remains constant because the inflow to  $S$  occurs at the same rate as the outflow from  $I$  (upper diagram) or from  $I_2$  (lower diagram).

We use two models of which compartmental flows are shown in Fig. 3.1. In the  $SI$  model (upper diagram), the population is divided into two infection categories— $S$  (susceptible) and  $I$  (infected). In the  $SI_1I_2$  model (lower diagram), the infectious period is divided into two compartments. In both  $SI$  and  $SI_1I_2$  models, the arrows to  $S$  represent the inflow of new susceptibles to the population at risk. Infection transmission is indicated by the arrow from  $S$  to  $I$  (or  $I_1$  in the  $SI_1I_2$  model). Death from infection (i.e. removal from the population at risk) is represented by the arrow coming out of  $I$  (or  $I_2$  in the  $SI_1I_2$  model). Death occurs at the same rate as an inflow of new susceptibles, which makes the population size remain constant.

#### 3.3.2 Duration of infection and transmission probability

In the  $SI$  model, duration of infection and transmission rates were arbitrarily chosen to highlight the interaction between partnership dynamics, the transmission

Table 3.1: Model parameters. For the  $SI$  model,  $\beta$  and  $\gamma$  are used without the subscript.

Symbol	Description
$\beta_i$	Transmission rate per person per day during stage $i$ for $i = 1, 2$ (1=PHI, 2=chronic stage).
$\gamma_i$	Progression rate per day from state $i$ to the next for $i = 1, 2$ (1=PHI, 2=chronic stage).
$\sigma$	Partnership dissolution rate per day.
$\rho$	Partnership formation rate per day.
$\mu$	Rate at which individuals leave the sexually active population.
$N$	Total population size.

rate, and the duration of infection. In the  $SI_1I_2$  model, they were chosen to model the course of HIV infection—primary HIV infection (PHI) and chronic stage. In this case, transmission rates were based on Pinkerton’s new analyses [36] of Rakai, Uganda study [34]. Per-act transmission probabilities were 0.03604 and 0.00084 during PHI and asymptomatic stage, respectively, given that the duration of PHI is 49 days. Duration of chronic stage was assumed to be 10 years. The lack of late peak in infectivity was chosen to take people who receive treatments into account, which is often the case in Western countries. Waiting time in each stage is exponentially distributed with means given above. Model parameters appear in Table 3.1.

Instead of transmission probabilities, we use transmission rate,  $\beta$ , which is the product of per-act transmission probability and the number of sex acts per unit time. Notice  $\beta$  is defined per person and thus the transmission rate per partnership,  $\lambda$ , is adjusted by the expected number of partners per person. That is, if an individual has  $n$  partners on average in the absence of HIV transmissions, then

$$\lambda = \beta/n. \tag{3.1}$$

That is,  $\lambda$  is varied by the expected number of partners per person in the absence of HIV transmissions,  $n$ , whereas  $\beta$  remains constant regardless of  $n$ . Here we implicitly

Table 3.2: State variables for the model

Symbol	Descriptions
$[i]$	Number of individuals in state $i$ for $i = S, I, I_1, I_2$ .
$[ij]$	Number of pairs of individuals in states $i$ and $j$ (labeled $i$ - $j$ pairs), respectively, for $i, j = S, I, I_1, I_2$ . $[ij] = [ji]$ . If $i = j$ , $[ij]$ indicates twice the number of $i$ - $j$ pairs

assume that the sex act rate per partner decreases proportionally to the number of expected partners. The assumption of fixed sex act rate per person appears to be more realistic than a fixed sex act rate per partnership regardless of the number of partners [62, 63]

### 3.3.3 Pair approximation

An overview about pair approximation (PA) is provided elsewhere [10]. Here we give a brief description. PA provides a way to model infection transmissions on networks using a system of ordinary differential equations (ODEs). In networks, infection outcomes of individuals depend on their immediate partners. Individuals with their partners form a set of pairs. Then, time evolution of pairs depends on triples. Time evolution of triples, in turn, depend on quadruples. This can go on until the whole network is modeled. In many cases, however, time evolution of individuals is well captured just by keeping track of pairs and approximating triples with pairs; hence the name *pair approximation*. Goodness of approximation can be assessed by comparing with the full stochastic model.

### 3.3.4 The $SI$ model

In the  $SI$  model following notations are used. The state of individuals is represented as  $i$ , where  $i = S, I$  indicates infection category. The number of individuals in state  $i$  is denoted by  $[i]$ . For example,  $[S]$  indicates the number of susceptibles.

Similar rules apply to pairs and triples. A pair of a susceptible and an infected is labeled as an  $S$ - $I$  pair and its number is represented by  $[SI]$ . A triple of a susceptible, an infected, and a susceptible is labeled as an  $S$ - $I$ - $S$  triple and its number is represented by  $[SIS]$ . In this case, the infected is connected to two susceptibles, but two susceptibles are not connected to each other. Note that pairs, triples, etc. are counted in both directions by convention. Thus, while  $[SI]$  means the number of  $S$ - $I$  pairs,  $[SIS]$  means *twice* the number of  $S$ - $I$ - $S$  triples.

Following ODEs describe the  $SI$  model. Time derivative of a variable of interest is expressed with a dot over the variable. We below provide detailed explanations for each equation.

$$\left. \begin{aligned} \dot{[S]} &= -\lambda[SI] + \gamma[I], \\ \dot{[I]} &= \lambda[SI] - \gamma[I], \\ \dot{[SS]} &= \rho[S][S]/N - \sigma[SS] - 2\lambda[SSI], \\ \dot{[SI]} &= \rho[S][I]/N - (\gamma + \sigma)[SI] + \lambda([SSI] - [SI] - [ISI]) \end{aligned} \right\} \quad (3.2)$$

Time evolution of the number of susceptibles is given as

$$\dot{[S]} = -\lambda[SI] + \gamma[I]. \quad (3.3)$$

The first term on the right-hand side,  $-\lambda[SI]$ , captures infection transmission in  $S$ - $I$  pairs.

The second term,  $\gamma[I]$ , indicates that new susceptibles are recruited every time death from infection occurs, which keeps the population size constant.

Time evolution of the number of  $S$ - $I$  pairs is given as

$$\dot{[SI]} = \rho[S][I]/N - (\gamma + \sigma)[SI] + \lambda(-[SI] - [ISI] + [SSI]), \quad (3.4)$$

where  $N = [I] + [S]$  means the total population size. The first term on the right-hand side captures partnership formation between susceptibles and infecteds. The next

term,  $-(\gamma + \sigma)[SI]$ , captures partnership dissolution and death of the infected in  $S-I$  pairs. The last term captures infection transmissions, where we need the terms that describe the number of triples. Transmissions in  $S-I$  pairs are captured by  $-\lambda[SI]$ . The next term,  $-\lambda[ISI]$ , captures transmission when the susceptible is connected to another infected. There are two  $S-I$  pairs in an  $I-S-I$  triple. Therefore, one may think a factor of two is needed. However,  $[ISI]$  indicates *twice* the number of  $I-S-I$  triples and thus we do not need a factor of two. The term,  $\lambda[SSI]$ , captures transmissions in case the susceptible is partnered to both an infected and a susceptible. This transmission turns an  $S-S$  pair into an  $S-I$  pair and thus increases the number of  $S-I$  pairs.

In Eqs. (3.3) and (3.4), we assume that new susceptible individuals enter the population at risk as single individuals whereas dying individuals may have partners. That is, the time evolution equation for  $S-I$  pairs does not include the inflow from  $I-I$  pairs that comes from instantaneously replacing infected deaths with susceptibles.

To close the system, we need to either model time evolution of triples or express triples with lower terms we have already modeled. One simple solution is to express the number of triples in terms of the number of pairs as follows:

$$[ijk] \approx [ij][jk]/[j]. \quad (3.5)$$

This approximation is based on the assumption that individuals in states  $i$  and  $k$  are independent over being partnered to individuals in state  $j$ . This is appropriate for the case where the number of partners per person follows a Poisson distribution [10]. In our case, errors involved in this approximation are negligible, as shown in Results section.

To express the  $[SSI]$  in terms of pairs, we need  $[SS]$ , of which time evolution is

given as

$$[\dot{S}S] = \rho[S][S]/N - 2\lambda[SSI] - \sigma[SS]. \quad (3.6)$$

As mentioned earlier,  $[SS]$  means *twice* the number of  $S$ - $S$  pairs. This is why we have a factor of two in the term,  $-2\lambda[SSI]$ .

### 3.3.5 The $SI_1I_2$ model

In the  $SI_1I_2$  model, following notations are used. The state of individuals is represented as  $i_j$ , where  $i = S, I$  and  $j = 1, 2$  indicate infection category and the stage of infection, respectively. The number of individuals in state  $i_j$  is denoted by  $[i_j]$ . Similarly,  $\lambda_j$  denotes the transmission rate per partnership from infecteds in stage  $j$ .

The following set of ODEs describe the  $SI_1I_2$  model. Since the  $SI_1I_2$  model is a simple extension of  $SI$  model, we do not provide explanations for equations.

$$\left. \begin{aligned} [\dot{S}] &= -\lambda_1[SI_1] - \lambda_2[SI_2] + \gamma_2[I_2], \\ [\dot{I}_1] &= \lambda_1[SI_1] + \lambda_2[SI_2] - \gamma_1[I_1], \\ [\dot{I}_2] &= \gamma_1[I_1] - \gamma_2[I_2], \\ [\dot{S}S] &= \rho[S][S]/N - 2(\lambda_1[SSI_1] + \lambda_2[SSI_2]) - \sigma[SS], \\ [\dot{S}I_1] &= \rho[S][I_1]/N + \lambda_1([SSI_1] - [I_1SI_1] - [SI_1]) \\ &\quad + \lambda_2([SSI_2] - [I_2SI_1]) - (\gamma_1 + \sigma)[SI_1], \\ [\dot{S}I_2] &= \rho[S][I_2]/N + \gamma_1[SI_1] - \lambda_1[I_1SI_2] - \lambda_2([I_2SI_2] + [SI_2]) \\ &\quad - (\gamma_2 + \sigma)[SI_2]. \end{aligned} \right\} \quad (3.7)$$

### 3.3.6 Correlation and average number of partners

To help derive and examine the basic reproductive ratio,  $\mathcal{R}_0$ , we use definitions on correlation between individuals and average number of partners. To derive  $\mathcal{R}_0$ , one assumes that the population remains entirely susceptible and thus we ignore that partnerships dissolve because of death from infection.

The correlation between individuals in states  $i$  and  $j$ ,  $\mathcal{C}_{ij}$ , is defined as

$$\mathcal{C}_{ij} \equiv \frac{N[ij]}{n[i][j]}, \quad (3.8)$$

where  $N$  and  $n$  indicate population size and the population-averaged number of partners per person [15]. We see that  $\mathcal{C}_{ij} \in [0, N]$ , and if  $\mathcal{C}_{ij} = 1$ , then individuals in states  $i$  and  $j$  are uncorrelated, meaning their being partnered to each other is random.

In this paper, we only use the correlation between susceptible and infected individuals:  $\mathcal{C}_{SI}$  ( $\mathcal{C}_{SI_1}$  and  $\mathcal{C}_{SI_2}$  in the  $SI_1I_2$  model). Notice these measures show the fraction of susceptible partners of infected individuals (by stage in the  $SI_1I_2$  model) relative to the population average. If they are one, the fraction of susceptible partners of infected individuals is the same as the fraction of susceptibles in the population. This arises in the well-mixed case. In the network model, these measures are usually below one. In other words, the probability an individual is susceptible given that this individual is partnered to an infected individual is lower than the probability a randomly chosen individual is susceptible.

After partnership dynamics reach a stationary point, if partnership dissolution because of death is not taken into account,  $n$  is given as:

$$\begin{aligned} N\rho &= 2P\sigma, \\ n &= 2P/N = \rho/\sigma, \end{aligned} \quad (3.9)$$



where  $P$  denotes the number of pairs.

During an endemic phase, the relationship does not hold because deaths of individuals also dissolve partnerships. For simplicity, however, we use the term *average number of partners* and  $n$  to refer to  $\rho/\sigma$ .

### 3.3.7 Background removal

In the model equations previously mentioned, we have assumed that individuals remain sexually active unless they die of AIDS. Lack of background removal simplifies  $\mathcal{R}_0$  derivation since it removes one parameter. However, the assumption that recruitment rate of susceptible individuals is a function of death rate is arbitrary and we relax this assumption in the final analyses of  $SI_1I_2$  model. We modified the model so that there is constant recruitment of susceptible individuals and all individuals stay sexually active for 25 years on average. In this case, individuals who die of AIDS are not replaced by susceptible individuals and so population size becomes smaller with death from AIDS.

## 3.4 Results

### 3.4.1 The $SI$ model

Time evolution of the number of infecteds is given as

$$\begin{aligned} \dot{[I]} &= \lambda[SI] - \gamma[I], \\ &= (n\lambda\mathcal{C}_{SI}[S]/N - \gamma)[I]. \end{aligned} \tag{3.10}$$

Since  $[S]$  is assumed to equal  $N$  initially,  $\mathcal{R}_0 = \beta/\gamma\mathcal{C}_{SI}$ . Recall  $\beta = n\lambda$ . As Fig. 3.2a illustrates,  $\mathcal{C}_{SI}$  is a dynamic variable. It is initially at one, meaning that susceptible and infected individuals are randomly partnered to each other, but then quickly converges to a *quasi-equilibrium* while the number of infected individuals

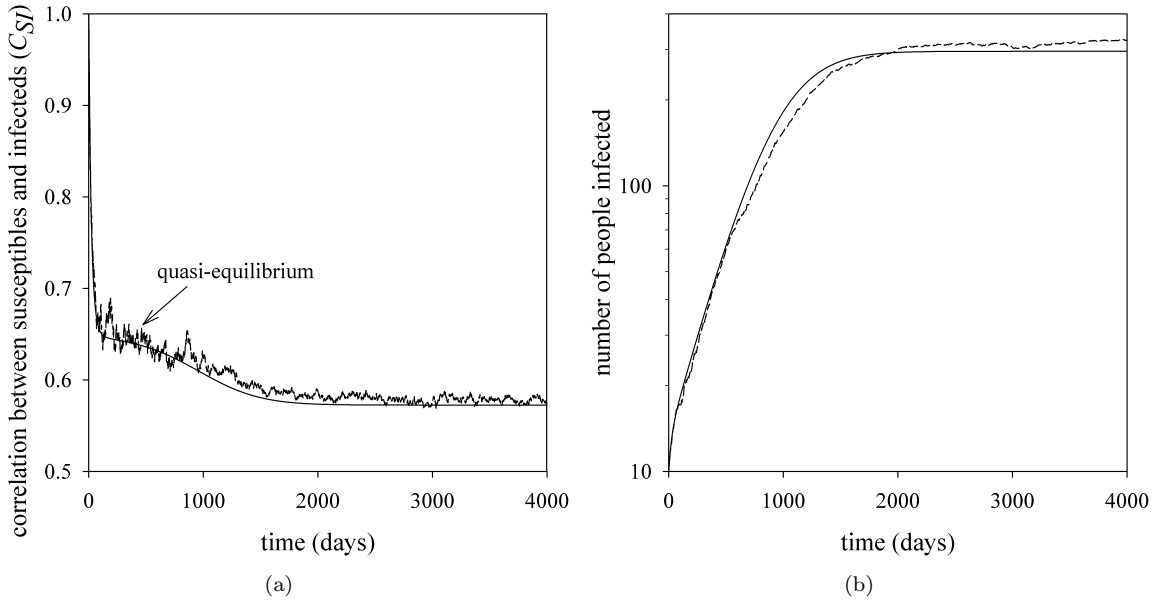


Figure 3.2: Results from pair approximation (solid line) and the average of 100 stochastic simulations (dashed line). (a) shows the correlation between susceptibles and infecteds,  $C_{SI}$ , (b) shows the number of infecteds on a base-10 logarithmic scale over time.  $C_{SI}$  quickly converges to a quasi-equilibrium ( $\sim 0.65$  in this particular case) while the number of infecteds grows exponentially.  $\rho = 0.02, \sigma = 0.01, \beta = 0.036, 1/\gamma = 49, N = 10000$

grows exponentially, as shown in Fig. 3.2b. This quasi-equilibrium has been used to derive  $\mathcal{R}_0$  both in fixed, regular networks [15] and in dynamic networks [16]. In this case,  $\mathcal{R}_0$  is better defined as the number of secondary infections generated by a single infected individual after the network structure between susceptible and infected individuals is established [15].

We now determine the quasi-equilibrium value of the correlation between susceptibles and infecteds,  $C_{SI}^*$ .

$$\begin{aligned}
 \dot{C}_{SI} &= \frac{N}{n} \frac{d}{dt} \left( \frac{[SI]}{[S][I]} \right) \\
 &= C_{SI} \left( \frac{[\dot{S}I]}{[SI]} - \frac{[\dot{I}]}{[I]} - \frac{[\dot{S}]}{[S]} \right) \\
 &\rightarrow \sigma + ((n-1)\lambda - \sigma)C_{SI} - \lambda n C_{SI}^2
 \end{aligned} \tag{3.11}$$

as  $[S]/N \rightarrow 1, [I]/N \rightarrow 0$ , and  $C_{SS} \rightarrow 1$ .

Letting  $\mathcal{C}_{SI}^* = 0$  gives

$$\mathcal{C}_{SI}^* = \frac{-(\sigma + \lambda(1 - n)) + \sqrt{(\sigma + \lambda(1 - n))^2 + 4\lambda\rho}}{2n\lambda}. \quad (3.12)$$

We first analytically examine  $\mathcal{C}_{SI}^*$  in two limiting cases—instantaneous or fixed partnerships—and then numerically analyze how it is influenced by the average number and the duration of partnerships.

First, for instantaneous partnerships, consider the limit where  $\sigma$  goes to infinity. To keep the average number of partners per person without death constant (i.e.,  $\rho/\sigma = \text{some constant } c$ ), we take  $\rho$  to infinity at the same rate. Replacing  $\sigma$  and  $\rho$  by  $\epsilon\sigma$  and  $\epsilon\rho$  and letting  $\epsilon$  go to infinity gives

$$\lim_{\epsilon \rightarrow \infty} \mathcal{C}_{SI}^* = 1, \quad (3.13a)$$

$$\lim_{\epsilon \rightarrow \infty} \mathcal{R}_0 = \beta/\gamma. \quad (3.13b)$$

This shows, if partnerships change rapidly, susceptibles and infecteds have no correlation and thus  $\mathcal{R}_0$  in the model with partnerships is the same as in the well-mixed case. That is, whether an epidemic will take off or die out is not affected by underlying networks in case partnerships change rapidly.

For fixed partnerships, consider the limit where  $\sigma$  goes to zero. Replacing  $\sigma$  and  $\rho$  by  $\epsilon\sigma$  and  $\epsilon\rho$  and let  $\epsilon$  go to zero gives

$$\lim_{\epsilon \rightarrow 0} \mathcal{C}_{SI}^* = 1 - 1/n, \quad (3.14a)$$

$$\lim_{\epsilon \rightarrow 0} \mathcal{R}_0 = (1 - 1/n)\beta/\gamma. \quad (3.14b)$$

This shows  $\mathcal{R}_0$  in a fixed network is smaller than in the well-mixed case by a factor of  $(1 - 1/n)$ . This also shows in the limit of large average number of partners per person (i.e.,  $n \rightarrow N \rightarrow \infty$ ), there is no correlation between susceptibles and infecteds and  $\mathcal{R}_0$  in the model with partnerships is again the same as in the well-mixed case.

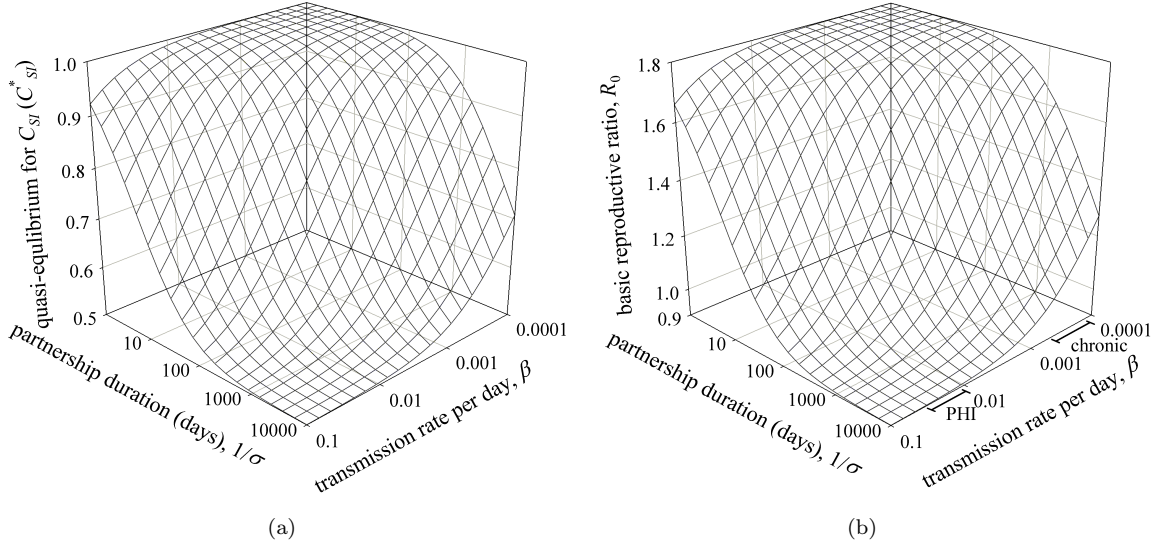


Figure 3.3: Quasi-equilibrium values of the correlation between susceptible and infected individuals,  $\mathcal{C}_{SI}^*$ , and basic reproductive ratios,  $\mathcal{R}_0$ , across partnership duration,  $1/\sigma$ , and transmission rate,  $\beta$ . (a) shows  $\mathcal{C}_{SI}^*$ , (b) shows  $\mathcal{R}_0$ . We correspondingly decrease  $\rho$  as we increase  $1/\sigma$  so that  $\rho/\sigma$  remains constant at 2. We also correspondingly increase  $\gamma$  as we increase  $\beta$  so that  $\beta/\gamma$  remains constant at 1.8.

A similar result has been derived for a regular fixed network in which  $\mathcal{R}_0 = (1 - 2/n)\beta/\gamma$  [15]. The difference— $(1 - 1/n)$  vs.  $(1 - 2/n)$ —arises because different assumptions were used to express the number of triples in terms of the number of pairs. In [15], the author used  $[ijk] = \zeta[ij][jk]/[j]$  with  $\zeta = (n - 1)/n$  whereas we used  $[ijk] = [ij][jk]/[j]$ . The former is appropriate for a regular, fixed network, but our assumption is appropriate for a Poisson random network [10].

Now let us examine  $\mathcal{C}_{SI}^*$  between the extremes of instantaneous and fixed partnerships. As Fig. 3.3a illustrates,  $\mathcal{C}_{SI}^*$  monotonically decreases with increasing partnership duration,  $1/\sigma$ . At a given  $\sigma$ , it decreases with increasing transmission rate  $\beta$ . We see that  $\mathcal{C}_{SI}^*$  approaches  $1/2$  (i.e.,  $1 - 1/n$  for  $n = 2$ ) as we increase  $1/\sigma$ . Since  $\mathcal{R}_0$  is given as a product of transmission potential and  $\mathcal{C}_{SI}^*$ , it has the same pattern as  $\mathcal{C}_{SI}^*$  at a given transmission potential,  $\beta/\gamma$ . This is seen in Fig. 3.3b. Decrease

in the transmission rate with a corresponding increase in the duration of infection increases  $\mathcal{R}_0$  in a network model where partnerships have a finite duration. Notice  $\mathcal{R}_0$  remains constant in instantaneous or fixed partnerships even if we vary  $\beta$  and  $\gamma$  at a given  $\beta/\gamma$ .

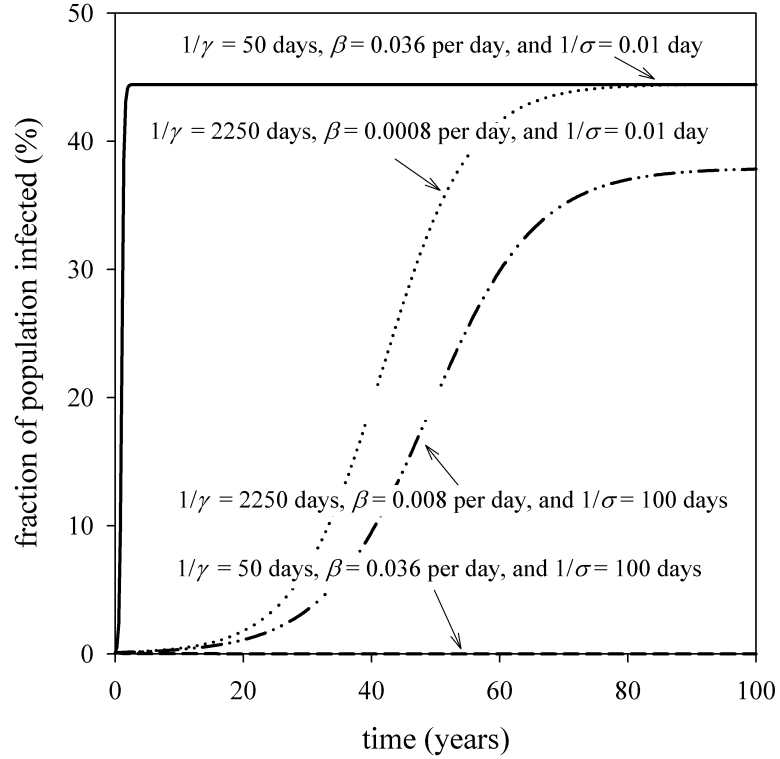


Figure 3.4: Fraction of population infected (%) over time. While the transmission rate,  $\beta$ , and the duration of infection,  $1/\gamma$ , are varied,  $\beta/\gamma$  remains constant at 1.8.

That  $\mathcal{R}_0$  increases with decreasing  $\beta$  with a corresponding increase in  $1/\gamma$  when partnerships have a positive finite duration can have a following implication. The chronic stage alone (i.e., lower  $\beta$  and higher  $1/\gamma$ ) can generate a major epidemic while PHI alone (i.e., higher  $\beta$  and lower  $1/\gamma$ ) dies out in some range of partnership duration even if the transmission potential is the same for both PHI and the chronic stage. To illustrate, we simulate following two scenarios. In one scenario, the duration of infection and transmission rate are set at 50 days and 0.036 per day, respectively. In

the other, transmission rate is decreased, but the duration of infection is increased by 45-fold each. Thus, the transmission potential is the same for both scenarios. We then set  $\sigma = 0.01$  or  $100$ , which gives on average  $0.01$  or  $100$  days of partnerships if partnership dissolution because of death is not taken into account. As shown in Fig. 3.4, endemic prevalence is the same for both scenarios if  $\sigma = 100$ . If  $\sigma = 0.01$ , however, endemic prevalence is markedly different between two scenarios—38% for lower  $\beta$  (e.g., chronic stage) vs. 0% for higher  $\beta$  (e.g., PHI).

### 3.4.2 The $SI_1I_2$ model

From Eq. (3.7), time evolution of the number of infected individuals with PHI is given as:

$$\begin{aligned} [\dot{I}_1] &= \lambda_1[SI_1] + \lambda_2[SI_2] - \gamma_1[I_1] \\ &= n \frac{[S]}{N} \left( \lambda_1 C_{SI_1} + \lambda_2 \frac{[I_2]}{[I_1]} C_{SI_2} - \gamma_1 \right) [I_1]. \end{aligned} \quad (3.15)$$

We assume that  $[S]$  equals  $N$  initially and so  $\mathcal{R}_0 = C_{SI_1}\beta_1/\gamma_1 + C_{SI_2}\beta_2[I_2]/[I_1]/\gamma_2$ .

We now derive quasi-equilibrium values for  $C_{SI_i}^*$ . While  $C_{SI_i}$  are at quasi-equilibrium, we also assume that  $[I_1^*]\gamma_1 = [I_2^*]\gamma_2$ , where  $[i^*]$  indicate the number of individuals in state  $i$  at quasi-equilibrium..

$$\begin{aligned} C_{SI_1}^* &= \frac{N}{n} \frac{d}{dt} \left( \frac{[SI_1]}{[S][I_1]} \right) \\ &= C_{SI} \left( \frac{[\dot{SI}_1]}{[SI_1]} - \frac{[\dot{I}_1]}{[I_1]} - \frac{[\dot{S}]}{[S]} \right) \\ &\rightarrow a_1 C_{SI_1}^2 + a_2 C_{SI_1} + a_3, \end{aligned} \quad (3.16)$$

where

$$\begin{aligned} a_1 &= -n\lambda_1, \\ a_2 &= (n-1)\lambda_1 - \sigma - C_{SI_2}n\lambda_2\gamma_1/\gamma_2 \\ a_3 &= \sigma + C_{SI_2}n\lambda_2\gamma_1/\gamma_2. \end{aligned}$$

Similarly,

$$\begin{aligned}
\mathcal{C}_{SI_2}^{\dot{}} &= \frac{N}{n} \frac{d}{dt} \left( \frac{[SI_2]}{[S][I_2]} \right) \\
&= \mathcal{C}_{SI_2} \left( \frac{[\dot{S}I_2]}{[SI_2]} - \frac{[\dot{I}_2]}{[I_2]} - \frac{[\dot{S}]}{[S]} \right) \\
&\rightarrow \sigma + \gamma_2 \mathcal{C}_{SI_1} - \mathcal{C}_{SI_2} (\lambda_2 + \gamma_2 + \sigma).
\end{aligned} \tag{3.17}$$

In Eqs. (3.16) and (3.17), letting  $\mathcal{C}_{SI_i}^{\dot{}} = 0$  gives two equations for two variables. As before, we analytically examine  $\mathcal{C}_{SI_i}^*$  in two limiting cases and then numerically examine how they are influenced by variable average number and durations of partnerships.

First, for instantaneous partnerships, consider the limit where  $\sigma$  goes to infinity. Again, we keep the average number of partners per person without death constant by taking  $\rho$  to infinity at the same rate as  $\sigma$ . Replacing  $\sigma$  and  $\rho$  by  $\epsilon\sigma$  and  $\epsilon\rho$  and letting  $\epsilon$  go to infinity gives

$$\lim_{\epsilon \rightarrow \infty} \mathcal{C}_{SI_i}^* = 1, \text{ for } i = 1, 2 \tag{3.18a}$$

$$\lim_{\epsilon \rightarrow \infty} \mathcal{R}_0 = \beta_1/\gamma_1 + \beta_2/\gamma_2. \tag{3.18b}$$

Again, if partnerships change rapidly, susceptible and infected individuals have no correlation and thus  $\mathcal{R}_0$  in the model with partnerships is the same as in the well-mixed case.

For fixed partnerships, we consider the limit where  $\sigma$  goes to zero. Replacing  $\sigma$

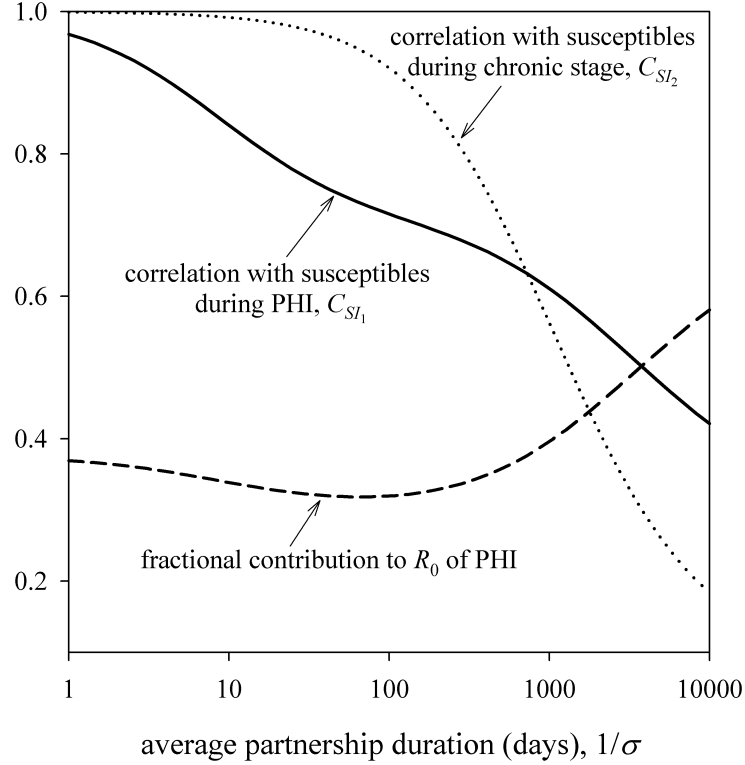


Figure 3.5: Quasi-equilibrium values of the correlation with susceptibles during PHI,  $\mathcal{C}_{SI_1}$ , or chronic stage,  $\mathcal{C}_{SI_2}$ , and fractional contribution to  $\mathcal{R}_0$  of PHI across partnership duration. The fractional contribution varies from 0 to 1, not from 0 to 100.  $\beta_1 = 0.036, \beta_2 = 0.00084, 1/\gamma_1 = 49$  and  $1/\gamma_2 = 3650$

and  $\rho$  by  $\epsilon\sigma$  and  $\epsilon\rho$  and letting  $\epsilon$  go to zero gives

$$\lim_{\epsilon \rightarrow 0} \mathcal{C}_{SI_1}^* = 1 - \frac{1}{n} \frac{\beta_1 \beta_2 / n + \beta_1 \gamma_2}{\beta_1 \beta_2 / n + \beta_1 \gamma_2 + \beta_2 \gamma_1}, \quad (3.19a)$$

$$\lim_{\epsilon \rightarrow 0} \mathcal{C}_{SI_2}^* = \left( \frac{\gamma_2}{\beta_2 / n + \gamma_2} \right) \mathcal{C}_{SI_1}^*, \quad (3.19b)$$

$$\lim_{\epsilon \rightarrow 0} \mathcal{R}_0 = \lim_{\epsilon \rightarrow 0} \mathcal{C}_{SI_1}^* \beta_1 / \gamma_1 + \lim_{\epsilon \rightarrow 0} \mathcal{C}_{SI_2}^* \beta_2 / \gamma_2. \quad (3.19c)$$

We see that  $\mathcal{C}_{SI_2}^*$  is always less than  $\mathcal{C}_{SI_1}^*$  for a finite  $n$ . Recall that  $\mathcal{C}_{SI_i}$  indicates the fraction of susceptible partners of infecteds in stage  $i$  relative to the population average.  $\mathcal{C}_{SI_2}^*$  will be less than  $\mathcal{C}_{SI_1}^*$  in fixed partnerships because infected partners during PHI become partners during chronic stage and the remaining susceptible partners are additionally infected during chronic stage. Thus, the fraction of susceptible partners



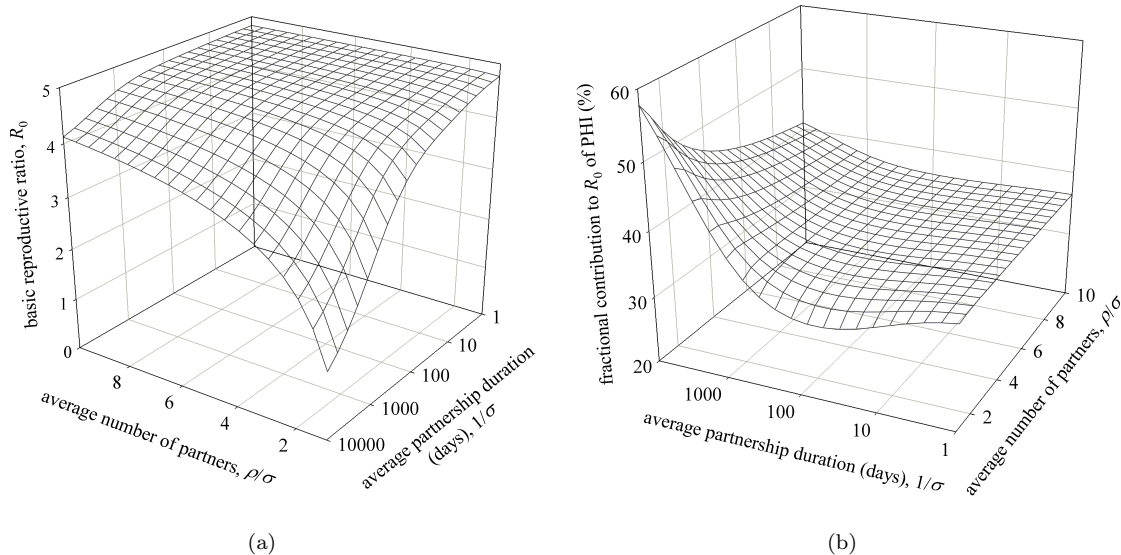


Figure 3.6: Basic reproductive ratio,  $\mathcal{R}_0$ , and the fractional contribution to  $\mathcal{R}_0$  of PHI (%) across partnership duration and average number of partners. (a) shows  $\mathcal{R}_0$  and (b) shows the fractional contribution to  $\mathcal{R}_0$  of PHI.  $\beta_1 = 0.036$ ,  $\beta_2 = 0.00084$ ,  $1/\gamma_1 = 49$  and  $1/\gamma_2 = 3650$

becomes lower during chronic stage than PHI.

In Fig. 3.5 we show how  $\mathcal{C}_{SI_i}^*$  changes by variable partnership durations. If partnership duration increases, the correlation with susceptibles becomes lower during PHI than chronic stage (i.e.,  $\mathcal{C}_{SI_1}^* < \mathcal{C}_{SI_2}^*$ ). As partnership duration continues to increase, however, correlation with the susceptible becomes higher during PHI than during chronic stage (i.e.,  $\mathcal{C}_{SI_1}^* > \mathcal{C}_{SI_2}^*$ ). The fractional contribution to  $\mathcal{R}_0$  of PHI,  $(\mathcal{C}_{SI_1}^* \beta_1 / \gamma_1) / (\mathcal{C}_{SI_1}^* \beta_1 / \gamma_1 + \mathcal{C}_{SI_2}^* \beta_2 / \gamma_2)$ , reflects this pattern—it initially drops fast, but rises as partnership duration increases.

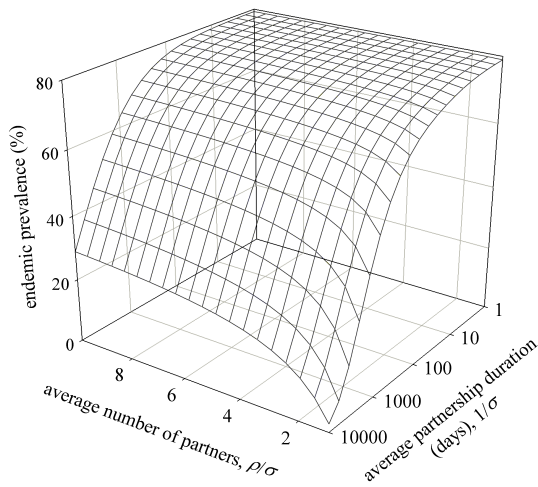
We have shown mechanisms underlying the change in fraction of transmissions over the stage of HIV infection across partnership durations and concurrencies in Chapter 2. Although we did not explicitly mention the correlation between susceptible and infected individuals in Chapter 2, mechanisms are the same. Initially lower  $\mathcal{C}_{SI_1}^*$  than  $\mathcal{C}_{SI_2}^*$  is mainly because transmission rate is higher during PHI than chronic

stage. That is, a higher transmission rate decreases the fraction of susceptible partners faster during PHI than the chronic stage. Later higher  $\mathcal{C}_{SI_1}^*$  than  $\mathcal{C}_{SI_2}^*$  arises because infected individuals with PHI progress to chronic stage while keeping their partners intact. This means partners infected during PHI are not replaced and transmissions additionally occur during chronic stage. Thus, the fraction of susceptible partners becomes lower during chronic stage than PHI.

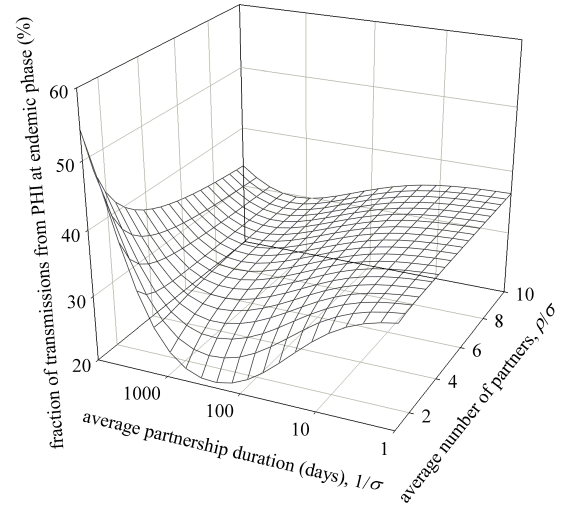
Figs. 3.6a and 3.6b show  $\mathcal{R}_0$  and the fractional contribution to  $\mathcal{R}_0$  of PHI across various durations and numbers of partnerships.  $\mathcal{R}_0$  decreases as partnership duration increases. At a given partnership duration, it is higher for a higher average number of partners. The fractional contribution to  $\mathcal{R}_0$  of PHI has a similar pattern—an initial decrease followed by a later increase—across the average number of partners. If the average number of partners is small (i.e., per-partnership transmission rate is high), both the initial decrease and the later increase are larger than when the average number of partners is large.

### 3.4.3 Endemic prevalence and the fraction of transmissions from PHI at endemic phase

As seen in Figs. 3.7a and 3.7b, endemic prevalence monotonically decreases as partnership duration increases or average number of partners decreases. The fraction of transmissions from PHI initially decreases, but later increases as partnership duration increases. Both the initial decrease and the later increase in the fraction of transmissions from PHI are larger for a smaller average number of partners than a large number of partners. The pattern of the fraction of transmissions from PHI is similar to the fractional contribution of PHI to  $\mathcal{R}_0$  seen in Fig. 3.6b. However, the fraction of transmissions from PHI at endemic phase is smaller than the fractional contribution to  $\mathcal{R}_0$  of PHI at a given duration and an average number of partnerships.

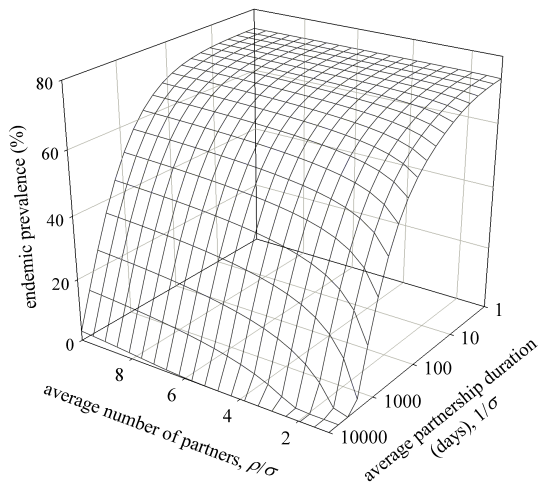


(a)

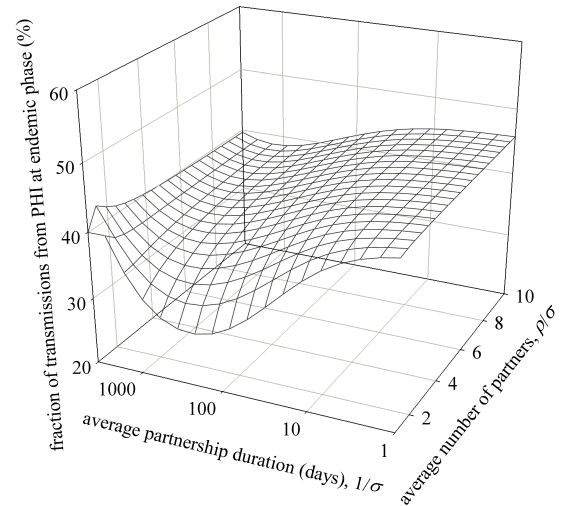


(b)

Figure 3.7: Endemic prevalence (%) and the fraction of transmissions from PHI (%) across variable durations and average numbers of partnerships. (a) shows endemic prevalence, (b) shows the fraction of transmissions from PHI at endemic phase.  $\beta_1 = 0.036, \beta_2 = 0.00084, 1/\gamma_1 = 49$  and  $1/\gamma_2 = 3650$



(a)



(b)

Figure 3.8: Endemic prevalence (%) and the fraction of transmissions from PHI (%) with background removal across variable durations and numbers of partnerships. (a) shows endemic prevalence, (b) shows the fraction of transmissions from PHI at endemic phase.  $\beta_1 = 0.036, \beta_2 = 0.00084, 1/\gamma_1 = 49, 1/\gamma_2 = 3650$  and  $1/\mu = 9125$

#### 3.4.4 Endemic prevalence and the fraction of transmissions from PHI at endemic phase with background removal

Fig. 3.8a shows endemic prevalence under various durations and numbers of partnerships when individuals remain sexually active for on average 25 years. Compared with the case without background removal (Fig. 3.7a), endemic prevalence is lower. This is natural since applying constant removal rate is the same as shortening the duration of infection, which reduces the transmission potential.

Fig. 3.8b illustrates the fraction of transmissions from PHI under various durations and numbers of partnerships. At a short partnership duration, the fraction is increased, compared with Fig. 3.7b (38% vs. 46%). That is, introducing background removal increases the *fraction of transmission potential* from PHI. Note that we are not saying that the *fraction of transmissions* from PHI increases with background removal. We are analyzing how much the fraction of transmissions from PHI changes from the fraction of transmission potential from PHI with various numbers and durations of partnerships. And, we have seen that the fraction of transmissions from PHI is almost the same as the fraction of transmission potential from PHI at short partnership duration.

Overall patterns of the fraction of transmissions from PHI at endemic phase—an initial decrease followed by a later increase—remain similar to the case without background removal. However, the fraction of transmissions from PHI never goes above the fraction of transmission potential ( $\sim 46\%$ ). This is partly because infection dies out at long partnership duration and so we can not assess the fraction of transmissions from PHI in long partnerships, where the fraction of transmissions from PHI can be bigger than its transmission potential (see Fig. 3.7b).

### 3.5 Discussion

We have shown that between the extremes of instantaneous and fixed partnerships, lower transmission rate for a longer duration of infection produces higher  $\mathcal{R}_0$  than higher transmission rate for a shorter duration of infection at a given transmission potential. This implies that long-term partnerships can decrease the fraction of transmissions from PHI (i.e., higher transmission rate over a shorter period) while increasing that from chronic stage (i.e., lower transmission rate over a longer period). Indeed, the fraction of transmissions from PHI drops with increasing partnership duration. It, however, increases again in longer partnerships.

Kretzschmar and Dietz [51] showed that the role of PHI can be small if partnerships are prolonged in serial monogamy. Our study shows that the role of PHI increases again in longer partnerships after an initial decrease in shorter partnerships. The difference comes from that they only examined serial monogamy whereas partnerships are concurrent in our model. Serial monogamy does not allow infection to spread through concurrent long-term partnerships where the fraction of transmissions from PHI is high.

The fraction of transmissions from PHI is also influenced by endemic prevalence. As shown in Figs. 3.6b and 3.7b, the fraction of transmissions from PHI at endemic phase is smaller than the fractional contribution to  $\mathcal{R}_0$  of PHI at a given duration and an average number of partnerships. Decreasing overall fraction of susceptibles seems to decrease the fraction of transmissions from PHI.

Our study has several limitations. First of all, we dealt only with random partnership formation and dissolution which lead to Poisson distribution of the number of partners in the limit of large population size. In reality, however, it appears that

sexual networks differ from Poisson distribution. For example, Liljeros *et al.* [64] showed that the number of partners over a year in a Swedish population roughly follows a Power-law distribution. And they argued that the *preferential attachment* may be a mechanism of sexual network formation, as has been claimed for other Power-law distributions such as World Wide Web [65]. Although it is debatable whether the Power-law distribution best describes the observed distribution of sexual networks and whether the preferential attachment is likely to be an underlying mechanism [66, 67], random partnership formation is unlikely to explain observed sexual networks. Therefore, various mechanisms and distributions other than random partnership formation need to be tried to account for real-world sexual networks.

Second, a population is in general better represented by a collection of heterogeneous subgroups than a single homogeneous population. For example, people are different regarding sex, the number of sex partners, languages they speak, etc. People with different characteristics generate complex mixing patterns rather than a single homogeneous mixing. Our inference about the role of transmissions during PHI may be significantly influenced by population structure. For example, the role of PHI has been shown to increase under more realistic population structure [44]. This study did not include long-term partnerships which we show can decrease the fraction of transmissions from PHI when partnerships last for a moderate duration (e.g., a few months to a few years). We are now pursuing assessing the role of PHI under more realistic population mixing patterns.

Third, the phase of an epidemic influences the role of PHI. We have examined the contribution of PHI during endemic phase or during an invasion period when the proportion of infected people is negligible. However, the contribution of PHI will be different depending on the phase of an epidemic. For example, while an

epidemic grows exponentially, the role of PHI is amplified. The main reason is that few individuals will have advanced to later infection during exponential growth phase [43, 44, 46].

Finally, if we take population heterogeneity into account, the role of each stage of HIV infection is likely to be different in each subgroup of the population. In a subgroup of population where the virus is recently introduced, the role of PHI will be amplified whereas it will be relatively smaller after endemic level of infection is achieved. Similarly, the role of PHI is larger in a subgroup of population where partnerships change rapidly compared with in a subgroup of population where partnerships are relatively stable.

## CHAPTER IV

### Sexual Role Segregation and HIV Transmissions by Stage

#### 4.1 Abstract

**Objective:** We sought to understand how sexual role segregation influences the transmission of human immunodeficiency virus (HIV) during primary HIV infection (PHI) and chronic infection in the context of dynamic sexual partnerships.

**Methods:** Using a system of ordinary differential equations with a pair approximation technique, we constructed models of HIV transmission in a heterosexual population in which partnerships form and break, and transmission rates vary by type of sex act—insertive and receptive sex acts.

**Results:** The basic reproductive ratio,  $\mathcal{R}_0$ , decreases with increasing partnership duration and with decreasing average number of partners. It also decreases with increasing difference in transmission rates between insertive and receptive sex acts. The fractional contribution to  $\mathcal{R}_0$  of PHI has a U-shaped relationship with increasing partnership duration. It drops in shorter partnerships (e.g., a few months to a few years) as partnership duration increases, but rises in longer partnerships (e.g., longer than a decade). At a given partnership duration, it monotonically increases with increasing average number of partners. It increases with decreasing difference in transmission rates between insertive and receptive sex acts. Endemic prevalence



has similar patterns to  $\mathcal{R}_0$ . The fraction of transmissions from PHI at endemic phase, however, is different from the fractional contribution to  $\mathcal{R}_0$  of PHI. It rarely changes with the difference in transmission rates between receptive and insertive sex acts. This seems to arise because the increase in endemic prevalence with decreasing difference in transmission rates between insertive and receptive sex acts counteracts the increase in the fraction of transmissions from PHI. If endemic prevalence remains the same, however, we expect the fraction of transmissions from PHI at endemic phase will decrease with increasing difference in transmission rates between insertive and receptive sex acts.

**Conclusions:** Endemic prevalence and the fraction of transmissions from PHI are influenced by the difference in transmission rates between insertive and receptive sex acts as well as partnership dynamics.

## 4.2 Introduction

Most models for the transmission of human immunodeficiency virus (HIV) have dealt with homosexual male population [43, 44, 68, 69, 70]. HIV transmissions are indeed more prevalent among homosexual males, especially in Western countries. For example, more than half of all newly diagnosed HIV infections (53%) in the U.S. in 2005 were among men who have sex with men [23]. Thus, modeling HIV transmissions in a homosexual population may be justified.

On the other hand, the majority of people living with HIV in sub-Saharan Africa (61%) are women. And about 90% of HIV infections in African adults are attributable to heterosexual contact [71]. Therefore, it is also necessary to model heterosexual transmissions of HIV. Furthermore, even in homosexual male population, people may take one sex role rather than the other (e.g., insertive vs. receptive

role). Transmission of HIV in a homosexual population in which individuals take either an insertive or a receptive role is essentially the same as the heterosexual transmission of HIV with transmission rates adjusted. Thus, from here onward, we use the term *heterosexual* to mean that there are two subpopulations and each subpopulation takes either an insertive or a receptive role. We call a subpopulation engaging in insertive sex acts males and that engaging in receptive sex acts females.

The heterosexual transmission is different from the homosexual transmission in a few aspects. In the heterosexual transmission, transmission rates can differ by the direction. For example, per-act transmission probability of HIV seems to be twice as high in receptive vaginal sex as in insertive one [72]. Similarly, a receptive anal sex is about eight times riskier than an insertive one [72]. Also, infected individuals in one subpopulation have to infect susceptibles in the other subpopulation first to sustain infection in their own subpopulation. For example, an infected male has to infect females first to increase infection in the male population.

Here we examine how the difference in transmission rates between insertive and receptive sex acts influence the transmission of HIV by stage of infection in the context of dynamic sexual partnerships. We compute the basic reproductive ratio,  $\mathcal{R}_0$ , and the fractional contribution to  $\mathcal{R}_0$  of primary HIV infection (PHI). We also numerically integrate the equations to evaluate the endemic prevalence and the fraction of transmissions from PHI at endemic phase.

### 4.3 Methods

#### 4.3.1 Compartmental flows for the model analyzed

Fig. 4.1 shows compartmental flows for the model analyzed. A population is composed of males (indexed by 1) and females (indexed by 2). Partnerships form only between opposite sex. In the *SI* model, where the infectious period is modeled as a

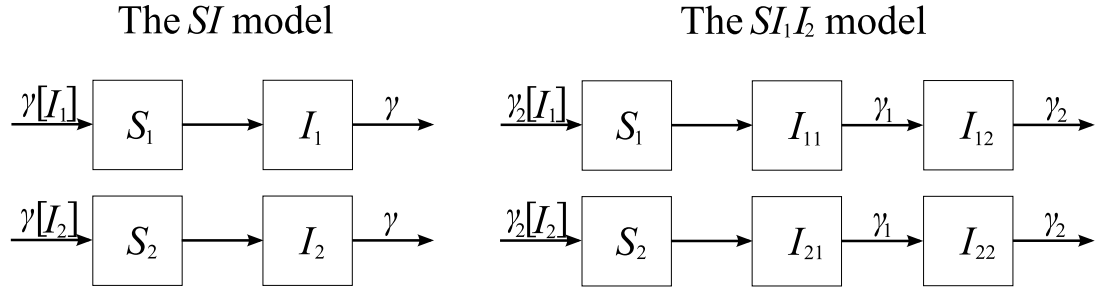


Figure 4.1: Compartmental flows for the model analyzed. In the  $SI$  model, the subscript indicates the sex of the individuals with 1 and 2 indicating male and female, respectively. In the  $SI_1I_2$  model,  $I_{ik}$  indicates infected individuals in stage  $k$  for  $k = 1, 2$ . An arrow from  $S_i$  to  $I_i$  (or  $I_{i1}$  in  $SI_1I_2$  model) indicates infection transmission. Population size remains constant because inflow to  $S_i$  occurs at the same rate as the outflow from  $I_i$  (or  $I_{i2}$  in  $SI_1I_2$  model)

Table 4.1: Model parameters. In the  $SI$  model,  $\beta_{ijk}$  and  $\gamma_k$  are used without subscript  $k$

Symbol	Description
$\beta_{ijk}$	Transmission rate per person per day from sex $j$ to $i$ during stage $k$ . $i, j = 1, 2$ and $i \neq j$ (1=male, 2=female) and $k = 1, 2$ (1=PHI, 2=chronic stage).
$\gamma_k$	Progression rate per day from stage $k$ to the next for $k = 1, 2$ (1=PHI, 2=chronic stage).
$\rho$	Partnership formation rate per day.
$\sigma$	Partnership dissolution rate per day.
$\mu$	Per-day rate of removal from the sexually active population.
$N$	Total population size.

single compartment, each male or female can be either  $S$  (susceptible) or  $I$  (infected). In the  $SI_1I_2$  model, where infectious period is modeled as two compartments, infected individuals are in either  $I_1$  or  $I_2$ .

#### 4.3.2 Duration of infection and transmission probability

In the  $SI$  model, duration of infection and transmission rates were arbitrarily chosen to highlight the interaction between partnership dynamics, transmission rate, duration of infection, and the difference in the transmission rate between insertive and receptive sex acts. In the  $SI_1I_2$  model, they were chosen to model the course of HIV infection—PHI and chronic stage. In this case, transmission rates were based on Pinkerton’s new analyses [36] of Rakai study [34]. Per-act transmission probabilities

are 0.03604 and 0.00084 during PHI and asymptomatic stage, respectively, given that the duration of PHI are 49 days. Duration of chronic stage was assumed to be 10 years.

Instead of per-act transmission probabilities, we use transmission rate, which is the product of per-act transmission probability and the number of sex acts per unit time. This simplifies the model by removing one parameter. We keep the ratio of transmission rates between PHI and chronic stage as the same as that in per-act transmission probabilities.

Difference in transmission rates between insertive and receptive sex acts are based on the study by Varghese *et al.* [72]. According to the study, receptive vaginal sex is twice as risky as insertive vaginal sex, per act. Also, receptive anal sex is about eight times riskier than the insertive anal sex.

To model the difference in transmission rates between insertive and receptive sex acts both in vaginal and in anal sex, we vary the ratio of transmission rate of receptive sex acts to that of insertive sex acts from one to ten while holding the sum of the two constant. For example, if transmission rates in insertive and receptive sex acts are  $\beta_{12}$  and  $\beta_{21}$ , respectively, we set  $\beta_{21} = r\beta_{12}$  for  $r = 1, 2, \dots, 10$  while keeping  $\beta_{12} + \beta_{21}$  at some constant  $c$ .

Finally, our definition of transmission rate,  $\beta$ , is per person and so the transmission rate per partnership,  $\lambda$ , is adjusted by the expected number of partnerships. That is, at a given  $\beta$ , if the expected number of partners per person is  $n$ , then

$$\lambda = \beta/n. \tag{4.1}$$

In other words, as we vary  $n$ ,  $\lambda$  is varied whereas  $\beta$  remains constant.

### 4.3.3 Pair approximation

An overview about pair approximation (PA) is provided elsewhere [10]. Here we give a brief description. PA provides a way to model infection transmissions on networks using a system of ordinary differential equations (ODEs). In networks, infection outcomes of individuals depend on their immediate partners. Individuals with their partners form a set of pairs. Then, time evolution of pairs depends on triples. Time evolution of triples, in turn, depend on quadruples. This can go on until the whole network is modeled. In many cases, however, time evolution of individuals is well captured just by keeping track of pairs and approximating triples with pairs; hence the name *pair approximation*. Goodness of approximation can be assessed by comparing with the full stochastic model.

### 4.3.4 The *SI* model

In the *SI* model following notations are used. The state of individuals is represented as  $i_j$ , where  $i \in \{S, I\}$  and  $j \in \{1, 2\}$  indicate the infection category and the sex of individuals with 1 and 2 meaning male and female, respectively. And  $\lambda_{ij}$  denotes the transmission rate in a partnership from an infected individual of sex  $j$  to a susceptible individual of sex  $i$ .

The number of individuals in state  $i_j$  is denoted by  $[i_j]$ . For example,  $[S_1]$  indicated the number of susceptible males. Similar rules apply to pairs and triples. A pair of a susceptible male and an infected female is labeled as an  $S_1-I_2$  pair and its number is represented by  $[S_1I_2]$ . A triple of a susceptible male, an infected female and an susceptible male is labeled as  $S_1-I_2-S_1$  and its number is represented by  $[S_1I_2S_1]$ . In this case, the infected female is connected to two susceptible males, but two susceptible males are not connected to each other. Note that pairs, triples, etc. are

counted in both directions by convention. Thus, while  $[S_1I_2]$  means the number of  $S_1$ - $I_2$  pairs,  $[S_1I_2S_1]$  means *twice* the number of  $S_1$ - $I_2$ - $S_1$  triples.

Following ODEs describe the  $SI$  model. Model parameters appear in Table 4.1. Time derivative of a variable of interest is expressed with a dot over the variable. We provide detailed explanations for the equations.

$$\left. \begin{aligned}
 [\dot{S}_1] &= -\lambda_{12}[S_1I_2] + \gamma[I_1], \\
 [\dot{I}_1] &= \lambda_{12}[S_1I_2] - \gamma[I_1], \\
 [S_1\dot{S}_2] &= \rho[S_1][S_2]/N - (\sigma[S_1S_2] + \lambda_{12}[I_2S_1S_2] + \lambda_{21}[S_1S_2I_1]), \\
 [S_1\dot{I}_2] &= \rho[S_1][I_2]/N + \lambda_{21}[S_1S_2I_1] \\
 &\quad - [S_1I_2](\sigma + \gamma + \lambda_{12}) - \lambda_{12}[I_2S_1I_2], \\
 [\dot{S}_2] &= -\lambda_{21}[S_2I_1] + \gamma[I_2], \\
 [\dot{I}_2] &= \lambda_{21}[S_2I_1] - \gamma[I_2], \\
 [S_2\dot{I}_1] &= \rho[S_2][I_1]/N + \lambda_{12}[S_2S_1I_2] \\
 &\quad - [S_2I_1](\sigma + \gamma + \lambda_{21}) - \lambda_{12}[I_1S_2I_1].
 \end{aligned} \right\} \quad (4.2)$$

Time evolution of the number of susceptible males is given as follows:

$$[\dot{S}_1] = -\lambda_{12}[S_1I_2] + \gamma[I_1]. \quad (4.3)$$

The first term on the right-hand side,  $-\lambda_{12}[S_1I_2]$ , captures infection transmission in  $S_1$ - $I_2$  pairs, i.e., pairs of a susceptible male and an infected female. Here  $\lambda_{12}$  denotes female-to-male (i.e., insertive) transmission rate. The second term,  $\gamma[I_1]$ , indicates that a new susceptible male is recruited every time an infected male is removed, which keeps the population size constant.

Time evolution of the number of  $S_1$ - $I_2$  pairs is given as follows:

$$[S_1\dot{I}_2] = \rho[S_1][I_2]/N - (\gamma + \sigma)[S_1I_2] - \lambda_{12}([S_1I_2] + [I_2S_1I_2]) + \lambda_{21}[S_1S_2I_1], \quad (4.4)$$

where  $N$  means the total population size including both females and males. The first term on the right-hand side,  $\rho[S_1][I_2]/N$ , captures partnership formation between susceptible males and infected females. The next term,  $(\gamma + \sigma)[S_1I_2]$ , captures partnership dissolution and stage progression of the infected female in  $S_1$ - $I_2$  pairs. Transmissions in  $S_1$ - $I_2$  pairs are captured by  $\lambda_{12}[S_1I_2]$ . The next term,  $\lambda_{12}[I_2S_1I_2]$ , captures transmission when the susceptible male is connected to another infected female. There are two  $S_1$ - $I_2$  pairs in an  $I_2$ - $S_1$ - $I_2$  triple. Therefore, one may think a factor of two is needed. However,  $[I_2S_1I_2]$  indicates *twice* the number of  $I_2$ - $S_1$ - $I_2$  triples and thus we do not need a factor of two. The term,  $\lambda_{21}[S_1S_2I_1]$ , captures male-to-female transmission in case the susceptible female is partnered to a susceptible male. This transmission turns an  $S_1$ - $S_2$  pair into an  $S_1$ - $I_2$  pair and thus increases the number of  $S_1$ - $I_2$  pairs.

As a final example, see the time evolution equation of  $S_1$ - $S_2$  pairs.

$$[S_1\dot{S}_2] = \rho[S_1][S_2]/N - \sigma[S_1S_2] - (\lambda_{12}[I_2S_1S_2] + \lambda_{21}[S_1S_2I_1]) \quad (4.5)$$

The first and second terms on the right-hand side capture partnership formation and dissolution, respectively. Male-to-female and female-to-male transmissions are captured in the next two terms.

Equations for  $[S_2\dot{S}_1]$  and  $[S_2\dot{I}_1]$  are the same as  $[S_1\dot{S}_2]$  and  $[S_1\dot{I}_2]$  except that the sex is reversed. Similarly, equations for  $[I_1\dot{S}_1]$  and  $[I_2\dot{S}_2]$  are the same as  $[S_1\dot{S}_2]$  and  $[S_2\dot{S}_1]$  with signs reversed.

In Eqs. (4.3) and (4.4), we assume that new susceptible individuals enter the population at risk as single individuals whereas dying individuals may have partners. That is, the time evolution equation for  $S_1$ - $I_2$  pairs does not include the inflow from  $I_1$ - $I_2$  pairs that comes from instantaneously replacing infected male deaths with susceptible male individuals.

To close the system, we need to either model time evolution of triples or express triples with other terms we have already modeled. One simple solution is to express the number of triples in terms of the number of pairs as follows:

$$[ijk] \approx [ij][jk]/[j]. \quad (4.6)$$

This approximation is based on the assumption that individuals in states  $i$  and  $k$  are independent over being partnered to individuals in state  $j$ . This is appropriate for the case where the number of partners per person follows Poisson distribution [10]. In our case, errors involved in this approximation are negligible, as shown in Results section.

#### 4.3.5 The $SI_1I_2$ model

In the  $SI_1I_2$  following notations are used. The state of individuals is represented as  $i_{jk}$ , where  $i \in \{S, I\}$ ,  $j \in \{1, 2\}$ ,  $k \in \{1, 2\}$  indicate the infection category, the sex of individuals, and the stage of infection, respectively. And  $\lambda_{ijk}$  denotes the transmission rate in a partnership from an infected individual of sex  $j$  in stage  $k$  to a susceptible individual of sex  $i$ .

Following ODEs describe the  $SI_1I_2$  model. Since the  $SI_1I_2$  model is a straightforward extension of the  $SI$  model, we do not give explanations for model equations.



$$\left. \begin{aligned}
[\dot{S}_1] &= -\lambda_{121}[S_1 I_{21}] - \lambda_{122}[S_1 I_{22}] + \gamma_2[I_{12}], \\
[\dot{I}_{11}] &= \lambda_{121}[S_1 I_{21}] + \lambda_{122}[S_1 I_{22}] - \gamma_1[I_{11}], \\
[\dot{I}_{12}] &= \gamma_1[I_{11}] - \gamma_2[I_{12}], \\
[S_1 \dot{S}_2] &= \rho[S_1][S_2]/N - \sigma[S_1 S_2] - \lambda_{121}[I_{21} S_1 S_2] - \lambda_{122}[I_{22} S_1 S_2] \\
&\quad - \lambda_{211}[S_1 S_2 I_{11}] - \lambda_{212}[S_1 S_2 I_{12}], \\
[S_1 \dot{I}_{21}] &= \rho[S_1][I_{21}]/N + \lambda_{211}[I_{11} S_1 S_2] + \lambda_{212}[I_{12} S_1 S_2] \\
&\quad - [S_1 I_{21}](\sigma + \gamma_1 + \lambda_{121}) - \lambda_{121}[I_{21} S_1 I_{21}] - \lambda_{122}[I_{22} S_1 I_{21}], \\
[S_1 \dot{I}_{22}] &= \rho[S_1][I_{22}]/N + \gamma_1[S_1 I_{21}] - [S_1 I_{22}](\sigma + \gamma_2 + \lambda_{122}) \\
&\quad - \lambda_{121}[I_{21} S_1 I_{22}] - \lambda_{122}[I_{22} S_1 I_{22}], \\
[\dot{S}_2] &= -\lambda_{211}[S_2 I_{11}] - \lambda_{212}[S_2 I_{12}] + \gamma_2[I_{22}], \\
[\dot{I}_{21}] &= \lambda_{211}[S_2 I_{11}] + \lambda_{212}[S_2 I_{12}] - \gamma_1[I_{21}], \\
[\dot{I}_{22}] &= \gamma_1[I_{21}] - \gamma_2[I_{22}], \\
[S_2 \dot{I}_{11}] &= \rho[S_2][I_{11}]/N + \lambda_{121}[I_{21} S_1 S_2] + \lambda_{122}[I_{22} S_1 S_2] \\
&\quad - [S_2 I_{11}](\sigma + \gamma_1 + \lambda_{211}) - \lambda_{211}[I_{11} S_2 I_{11}] - \lambda_{212}[I_{12} S_2 I_{11}], \\
[S_2 \dot{I}_{12}] &= \rho[S_2][I_{12}]/N + \gamma_1[S_2 I_{11}] \\
&\quad - [S_2 I_{12}](\sigma + \gamma_2 + \lambda_{212}) - \lambda_{211}[I_{11} S_2 I_{12}] - \lambda_{212}[I_{12} S_2 I_{12}].
\end{aligned} \right\} \quad (4.7)$$

#### 4.3.6 Correlation and average number of partners

To help derive and examine the basic reproductive ratio,  $\mathcal{R}_0$ , we use definitions on correlation between individuals and average number of partners. To derive  $\mathcal{R}_0$ , one assumes that the population remains entirely susceptible and thus we ignore that partnerships dissolve because of death from infection. We also assume that the size of male population is the same as the size of female population.

The correlation between individuals in states  $i$  and  $j$ ,  $\mathcal{C}_{ij}$ , is defined as

$$\mathcal{C}_{ij} \equiv \frac{n}{F} \frac{[ij]}{[i][j]}, \quad (4.8)$$

where  $n$  indicates the average number of male partners per female (or vice versa).  $F$  indicates the number of females and is assumed to equal the number of males. A Thus, from here onward, we use  $F$  to indicate the size of male or female population. Since partnerships form between opposite sex, the sex of individuals in state  $i$  must be different from that of individuals in state  $j$ .

In this paper, we only use the correlation between susceptible and infected individuals:  $\mathcal{C}_{S_i I_j(k)}$ . Notice these measures show the fraction of susceptible male (female) partners of a female (male) infected individual (by stage in the  $SI_1I_2$  model) relative to the population average. If they are one, the fraction of susceptible partners of infected individuals is the same as the fraction of susceptibles in the population. This arises in the “well-mixed” case. In the network model, these measures are usually below one. This means the probability an individual is susceptible given that this individual is partnered to an infected individual is lower than the probability a randomly chosen individual is susceptible.

After partnership dynamics reach a stationary point, the expected number of partners per person without death,  $n$ , is computed as follows:

$$P\sigma = \rho MF/N, \quad (4.9a)$$

$$n = P/M = P/F = \rho/2/\sigma, \quad (4.9b)$$

where  $P$  indicates the number of pairs. This indicates the expected number of partners per person in our heterosexual transmission model (i.e.,  $\rho/2/\sigma$ ) is half that in a homosexual population (i.e.,  $\rho/\sigma$ ) at given  $\rho$  and  $\sigma$ . In other words, only half of the population is potential partners for any individual.

During an endemic phase, however, the relationship does not hold because deaths of individuals also dissolve partnerships. For simplicity, however, we use the term *average number of partners* and  $n$  to refer to  $\rho/2/\sigma$ .

#### 4.3.7 Background removal

In the model equations previously mentioned, we have assumed that individuals remain sexually active unless they die of AIDS. Lack of background removal simplifies  $\mathcal{R}_0$  derivation since it removes one parameter. However, the assumption that recruitment rate of susceptible individuals is a function of death rate is arbitrary and we relax this assumption in the final analyses of  $SI_1I_2$  model. We modified the model so that there is constant recruitment of susceptible individuals and all individuals stay sexually active for 25 years on average. In this case, individuals who die of AIDS are not replaced by susceptible individuals and so population size becomes smaller with death from AIDS.

#### 4.3.8 Algebraic calculation and numerical integration

Numerical integrations were done using MATLAB<sup>®</sup> (7.0.1.24704, The MathWorks, Natick, MA). Algebraic calculations were done using MATLAB with Symbolic Math Toolbox<sup>™</sup> 5. In particular, numerical integrations were done using “ode45” function, algebraic solutions were obtained using “solve” function, and the limit properties of correlation measures and basic reproductive ratios were obtained using “limit” function.

### 4.4 Results

#### 4.4.1 $\mathcal{R}_0$ for the $SI$ model

Computation of  $\mathcal{R}_0$  follows the procedure given in Diekmann *et al.* [73]. We first count the number of secondary infections in the female (or male) population

generated by a newly infected male (or female) individual during its infectious period. The resulting  $2 \times 2$  matrix is called the “next-generation operator” and  $\mathcal{R}_0$  equals the dominant eigenvalue of this matrix.

As an example, consider secondary infections in the female population by an infected male. The instantaneous rate is

$$\lambda_{21}[S_2 I_1]/[I_1] = \frac{[S_2]}{F} n \lambda_{21} \mathcal{C}_{S_2 I_1}. \quad (4.10)$$

Then, we just need to multiply with the duration of infection,  $1/\gamma$ , to get the number of secondary infections in the female population by a male during its entire infectious period. The number of secondary infections in the male population by a female is computed similarly.

Thus, the next-generation operator  $M$  for this heterosexual  $SI$  model is

$$\begin{pmatrix} 0 & m_{12} \\ m_{21} & 0 \end{pmatrix}, \quad (4.11)$$

where

$$m_{ij} = \frac{[S_i]}{F} \mathcal{C}_{S_i I_j} \beta_{ij} / \gamma.$$

Recall  $\beta_{ij} = n \lambda_{ij}$ . Here  $m_{ij}$  indicates the number of secondary infections in the population of sex  $i$  generated by a newly infected individual of sex  $j$  during its entire infectious period. Note  $m_{11} = m_{22} = 0$  because transmissions occur only through heterosexual “contact”. Recall  $F$  can be replaced with  $M$ , the male population size. We see that the only difference between the model with partnerships and the well-mixed model is  $\mathcal{C}_{S_i I_j}$ .

The dominant eigenvalue of  $M$  is

$$\sqrt{m_{12} m_{21}}. \quad (4.12)$$

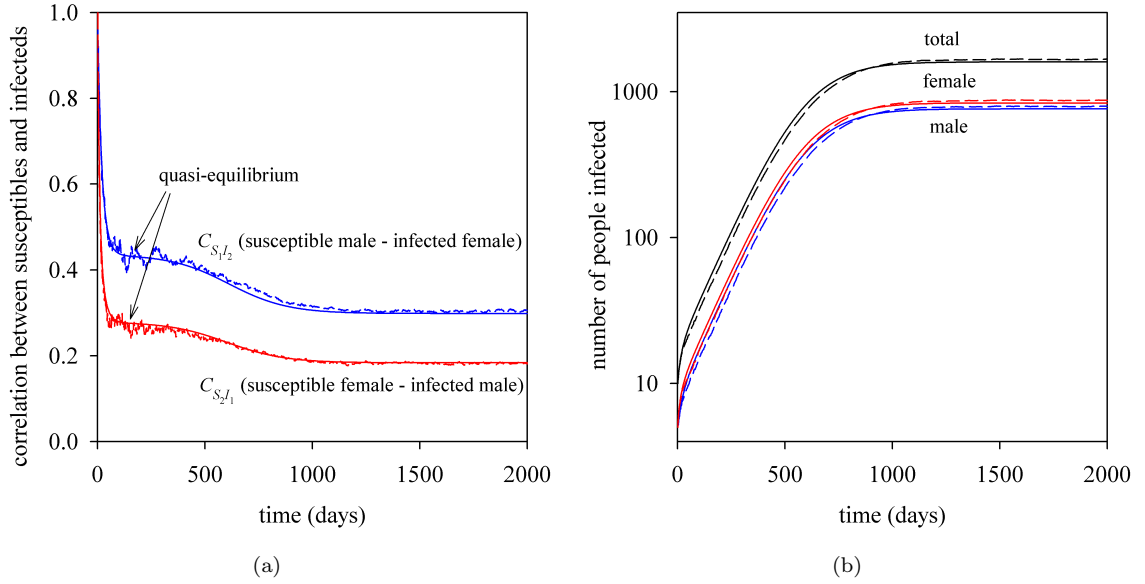


Figure 4.2: Results from pair approximation (solid line) and the average of 100 stochastic simulations (dashed line). (a) shows the correlation between susceptible and infected individuals ( $C_{S_1 I_2}$  and  $C_{S_2 I_1}$ ), (b) shows the number of infected individuals on a base-10 logarithmic scale over time. Correlations quickly converge to quasi-equilibrium values while the numbers of infected individuals grow exponentially.  $\rho = 0.02$ ,  $\sigma = 0.01$ ,  $\beta_{21} = 2 \times \beta_{12} = 0.072$ ,  $\gamma = 0.01$ ,  $N = 10000$

That is,  $\mathcal{R}_0$  is the same as the geometric mean of  $m_{ij}$ .

Since  $[S_i]$  is assumed to be  $F$  initially,

$$\mathcal{R}_0 = \sqrt{\beta_{12}\beta_{21}C_{S_1 I_2}C_{S_2 I_1}}/\gamma. \quad (4.13)$$

As Fig. 4.2a illustrates,  $C_{S_i I_j}$  is a dynamic variable. It is initially at one meaning susceptible and infected individuals are randomly partnered to each other, but then drops fast to a quasi-equilibrium value,  $C_{S_i I_j}^*$ . The quasi-equilibrium value indicates the initial establishment of local network structure [15] and has been used to compute  $\mathcal{R}_0$  both in regular, fixed [15] and dynamic networks [16]. We also use  $C_{S_i I_j}^*$  to compute  $\mathcal{R}_0$ , which, in this case, is more appropriately interpreted as the number of secondary infections after the local network structured has been established [15].

We now describe how to compute  $C_{S_i I_j}^*$ . Under the assumptions of  $I_i/F \rightarrow$

$0, \mathcal{C}_{S_i S_j} = 1$ , and  $S_i/F \rightarrow 1$ ,

$$\begin{aligned} \dot{\mathcal{C}}_{S_1 I_2} &= \frac{F}{n} \frac{d}{dt} \left( \frac{[S_1 I_2]}{[S_1][I_2]} \right) \rightarrow \\ &\sigma + \mathcal{C}_{S_2 I_1} \beta_{21} - \mathcal{C}_{S_1 I_2} (\sigma + \mathcal{C}_{S_2 I_1} \beta_{21} + \beta_{12}/n) \end{aligned} \quad (4.14a)$$

$$\begin{aligned} \dot{\mathcal{C}}_{S_2 I_1} &= \frac{F}{n} \frac{d}{dt} \left( \frac{[S_2 I_1]}{[S_2][I_1]} \right) \rightarrow \\ &\sigma + \mathcal{C}_{S_1 I_2} \beta_{12} - \mathcal{C}_{S_2 I_1} (\sigma + \mathcal{C}_{S_1 I_2} \beta_{12} + \beta_{21}/n) \end{aligned} \quad (4.14b)$$

Letting  $\dot{\mathcal{C}}_{S_i I_j} = 0$  gives

$$\mathcal{C}_{S_1 I_2}^* = \frac{-b + \sqrt{b^2 - 4ac}}{2a}, \quad (4.15)$$

where

$$a = \beta_{12} (\beta_{21} + \sigma + \beta_{12}/n),$$

$$b = -\beta_{21} (\beta_{12} - \sigma) + (\sigma + \beta_{21}/n)(\sigma + \beta_{12}/n) - \beta_{12}\sigma,$$

$$c = -\sigma(\beta_{21} + \beta_{21}/n + \sigma).$$

We get  $\mathcal{C}_{S_2 I_1}^*$  by plugging  $\mathcal{C}_{S_1 I_2}^*$  into Eqs. (4.14a) or (4.14b).

The solutions for  $\mathcal{C}_{S_i I_j}^*$  and thus  $\mathcal{R}_0$  are not easily simplified except for two limiting cases—instantaneous or fixed partnerships.

For instantaneous partnerships, consider the limit where  $\sigma$  goes to infinity. To keep the average number of partners per person in the absence of transmissions constant (i.e.,  $\rho/2/\sigma$  some constant  $c$ ), we take  $\rho$  to infinity at the same rate. Replacing  $\sigma$  and  $\rho$  by  $\epsilon\sigma$  and  $\epsilon\rho$  and letting  $\epsilon$  go to infinity gives

$$\lim_{\epsilon \rightarrow \infty} \mathcal{C}_{S_i I_j}^* = 1, \quad (4.16a)$$

$$\lim_{\epsilon \rightarrow \infty} \mathcal{R}_0 = \sqrt{\beta_{12}\beta_{21}}/\gamma. \quad (4.16b)$$

If insertive and receptive transmission rates are the same (i.e.,  $\beta_{12} = \beta_{21}$ ),  $\mathcal{R}_0$  becomes  $\beta_{ij}/\gamma$ , which is the same as in the well-mixed model.

For fixed partnerships, consider the limit where  $\sigma$  goes to zero. Replacing  $\sigma$  and  $\rho$  by  $\epsilon\sigma$  and  $\epsilon\rho$  and letting  $\epsilon$  go to zero gives

$$\lim_{\epsilon \rightarrow 0} \mathcal{C}_{S_1 I_2} = \left(1 - \frac{1}{n}\right) \frac{(n+1)\beta_{21}}{n\beta_{21} + \beta_{12}}, \quad (4.17a)$$

$$\lim_{\epsilon \rightarrow 0} \mathcal{C}_{S_2 I_1} = \left(1 - \frac{1}{n}\right) \frac{(n+1)\beta_{12}}{n\beta_{12} + \beta_{21}}, \quad (4.17b)$$

$$\lim_{\epsilon \rightarrow 0} \mathcal{R}_0 = \left(1 - \frac{1}{n}\right) \frac{1}{\gamma} \sqrt{\frac{((n+1)\beta_{12}\beta_{21})^2}{(n\beta_{12} + \beta_{21})(n\beta_{21} + \beta_{12})}}. \quad (4.17c)$$

Again, if  $\beta_{12} = \beta_{21}$ , then  $\mathcal{R}_0$  is

$$(1 - 1/n)\beta_{ij}/\gamma, \quad (4.18)$$

which is the same as in the homosexual population case in Chapter 3. That is, we recover  $\mathcal{R}_0$  of the homosexual population case by setting transmission rates are the same in both insertive and receptive sex acts.

This shows  $\mathcal{R}_0$  in a fixed network is smaller than in the well-mixed case. This also shows that in the limit of large  $n$ , the correlation between susceptibles and infecteds is one and  $\mathcal{R}_0$  in the model with partnerships is again the same as in the well-mixed case.

Between the extremes of instantaneous and fixed partnerships, we study  $\mathcal{C}_{S_i I_j}^*$  numerically. We first show how  $\mathcal{C}_{S_i I_j}^*$  and  $\mathcal{R}_0$  vary by transmission rate and partnership duration. As shown in Figs. 4.3a and 4.3b, correlations decrease as transmission rate increases and as partnership duration increases. Note we correspondingly decrease new partnership formation rate,  $\rho$ , as we increase partnership duration,  $1/\sigma$ , so that average number of partners,  $\rho/2/\sigma$ , remains constant. Since transmission rate is higher in receptive than in insertive sex acts (in this case, eight times higher), correlation between susceptible females and infected males (Fig. 4.3a) is lower than that between susceptible males and infected females (Fig. 4.3b).

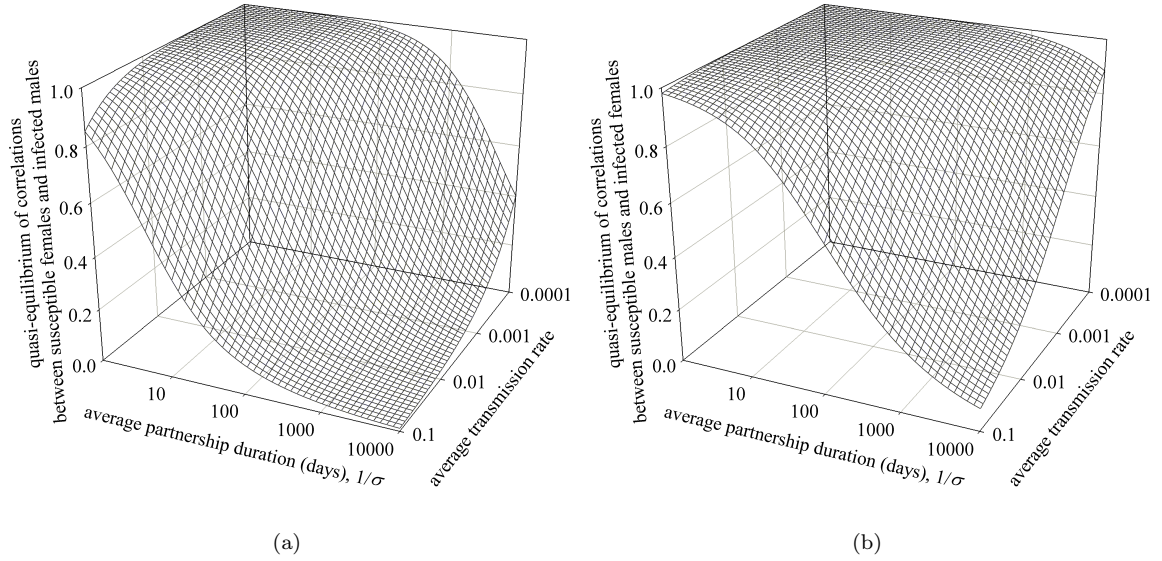


Figure 4.3: Quasi-equilibrium values for the correlation between susceptible and infected individuals under various average numbers of partners and average transmission rates. (a) and (b) show quasi-equilibrium values for the correlation between susceptible females and infected males, and the correlation between susceptible males and infected females, respectively. Average transmission rate means  $(\beta_{21} + \beta_{12})/2$ .  $\beta_{21} = 8 \times \beta_{12}$ ,  $\rho/\sigma = 2$ ,  $1/\gamma = 100$ .

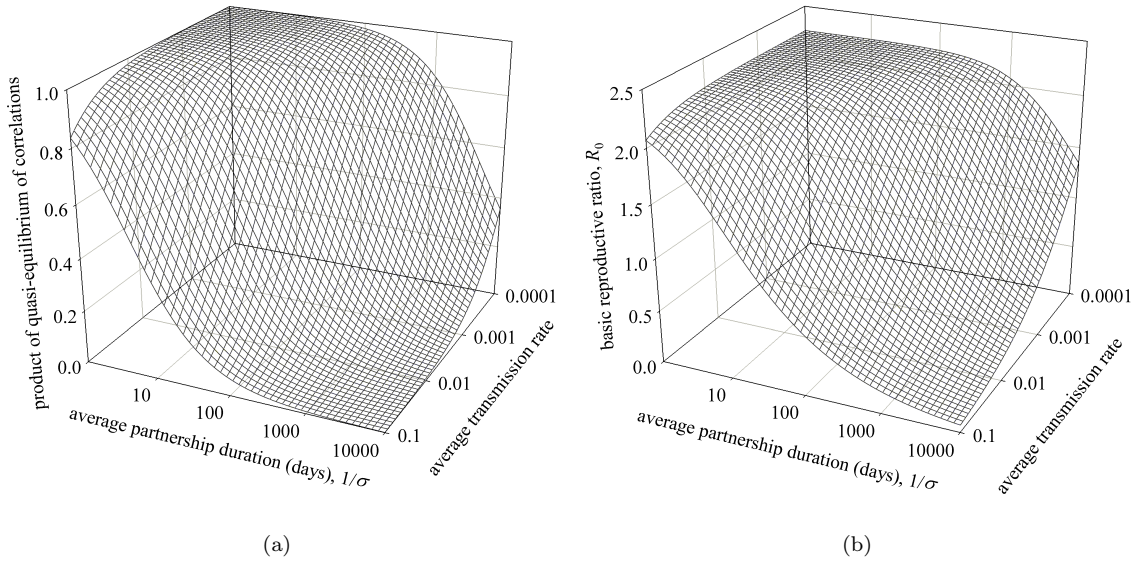


Figure 4.4: Product of quasi-equilibrium values for the correlation between susceptible and infected individuals and  $\mathcal{R}_0$  under various average number of partners and average transmission rates. (a) shows the product of quasi-equilibrium values for the correlation between susceptible and infected individuals, (b) shows  $\mathcal{R}_0$ . Average transmission rate means  $(\beta_{21} + \beta_{12})/2$ .  $\beta_{21} = 8 \times \beta_{12}$ ,  $\rho/\sigma = 2$ ,  $1/\gamma = 100$ . For  $\mathcal{R}_0$ ,  $\gamma$  was varied as  $\beta_{ij}$  is varied so that  $(\beta_{12} + \beta_{21})/\gamma$  remains at 7.2.



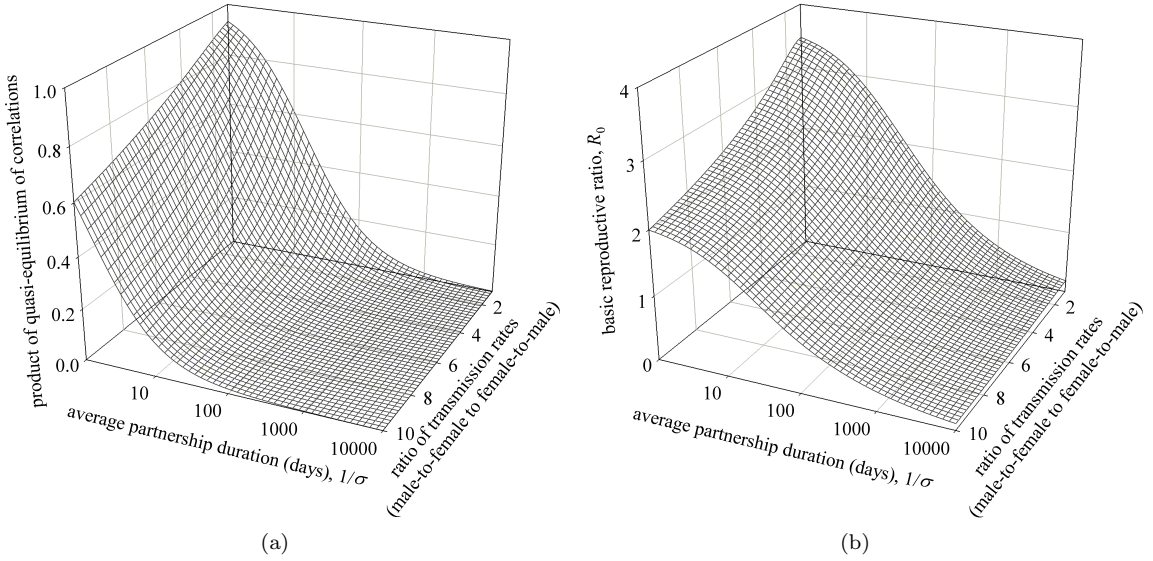


Figure 4.5: Product of correlations and  $\mathcal{R}_0$  across partnership duration and the ratio of transmission rates (male-to-female to female-to-male). (a) shows the product of the correlations,  $\mathcal{C}_{S_1 I_2}^* \mathcal{C}_{S_2 I_1}^*$ , (b) shows  $\mathcal{R}_0$ .  $\rho/2/\sigma = 1$ ,  $(\beta_{21} + \beta_{12})/2 = 0.036$ ,  $\gamma = 0.01$ ,  $N = 10000$

Fig. 4.4a shows the product of correlations (i.e.,  $\mathcal{C}_{S_1 I_2}^* \mathcal{C}_{S_2 I_1}^*$ ) across partnership duration and transmission rates. Since  $\mathcal{R}_0$  is proportional to the product of correlations (see Eq. (4.13)), it has similar patterns, as seen in Fig. 4.4b. It increases with decreasing transmission rate and with decreasing partnership duration. Here we keep the transmission potential, the product of transmission rate and the duration of infection, constant. Note  $\mathcal{R}_0$  will not change by the change in duration of infection or transmission rate if partnerships are fixed or instantaneous at a given transmission potential.

Now consider a situation where the sum of  $\beta_{12}$  and  $\beta_{21}$  remains constant while the ratio (or the difference) between them varies. In particular, we set  $\beta_{21} = r\beta_{12}$  for  $r = 1, 2, \dots, 10$ . Fig. 4.5a shows that the product of  $\mathcal{C}_{S_1 I_2}^*$  and  $\mathcal{C}_{S_2 I_1}^*$  is maximal when  $\beta_{12} = \beta_{21}$  (i.e.,  $r = 1$ ). Since the product of transmission rates,  $\beta_{12}\beta_{21}$ , is also maximal when  $\beta_{12} = \beta_{21}$ ,  $\mathcal{R}_0$  from Eq. (4.13) is maximal when  $\beta_{12} = \beta_{21}$ . This is

shown in Fig. 4.5b.

This shows that an epidemic in a heterosexual population is more likely to occur when transmission rates do not vary by types of sex acts given that total transmission rates in the population remain constant.

#### 4.4.2 $\mathcal{R}_0$ for the $SI_1I_2$ model

The next-generation operator  $M$  for the  $SI_1I_2$  model is

$$\begin{pmatrix} 0 & m_{12} \\ m_{21} & 0 \end{pmatrix}, \quad (4.19)$$

where

$$m_{ij} = \sum_{k=1}^2 \frac{[S_i]}{F} \beta_{ijk} \mathcal{C}_{S_i I_{jk}} / \gamma_k.$$

Here  $m_{ij}$  indicates the number of new infections of sex  $i$  generated by a newly infected individual of sex  $j$  during its entire infectious period.

As  $[S_i]$  is assumed to be  $F$  initially,  $\mathcal{R}_0$  is

$$\sqrt{\sum_{k=1}^2 \beta_{12k} \mathcal{C}_{S_1 I_{2k}} / \gamma_k \sum_{k=1}^2 \beta_{21k} \mathcal{C}_{S_2 I_{1k}} / \gamma_k}. \quad (4.20)$$

We now compute the quasi-equilibrium values for correlations. Under the assump-

tions of  $I_{ij}/F \rightarrow 0$ ,  $\mathcal{C}_{S_i S_j} = 1$ ,  $S_i/F \rightarrow 1$ ,  $I_{1j} = I_{2j}$ , and  $I_{i1}\gamma_1 = I_{i2}\gamma_2$ ,

$$\begin{aligned} \mathcal{C}_{S_1 I_{21}}^\cdot &= \frac{F}{n} \frac{d}{dt} \left( \frac{[S_1 I_{21}]}{[S_1][I_{21}]} \right) \rightarrow \\ &\sigma + \mathcal{C}_{S_2 I_{11}} \beta_{211} + \mathcal{C}_{S_2 I_{12}} \beta_{212} (\gamma_1/\gamma_2) \\ &\quad - \mathcal{C}_{S_1 I_{21}} (\sigma + \beta_{121}/n + \mathcal{C}_{S_2 I_{11}} \beta_{211} + \mathcal{C}_{S_2 I_{12}} \beta_{212} (\gamma_1/\gamma_2)) \end{aligned} \quad (4.21a)$$

$$\begin{aligned} \mathcal{C}_{S_1 I_{22}}^\cdot &= \frac{F}{n} \frac{d}{dt} \left( \frac{[S_1 I_{22}]}{[S_1][I_{22}]} \right) \rightarrow \\ &\sigma + \mathcal{C}_{S_1 I_{21}} \gamma_2 - \mathcal{C}_{S_1 I_{22}} (\sigma + \gamma_2 + \beta_{122}/n) \end{aligned} \quad (4.21b)$$

$$\begin{aligned} \mathcal{C}_{S_2 I_{11}}^\cdot &= \frac{F}{n} \frac{d}{dt} \left( \frac{[S_2 I_{11}]}{[S_2][I_{11}]} \right) \rightarrow \\ &\sigma + \mathcal{C}_{S_1 I_{21}} \beta_{121} + \mathcal{C}_{S_1 I_{22}} \beta_{122} (\gamma_1/\gamma_2) \\ &\quad - \mathcal{C}_{S_2 I_{11}} (\sigma + \beta_{211}/n + \mathcal{C}_{S_1 I_{21}} \beta_{121} + \mathcal{C}_{S_1 I_{22}} \beta_{122} (\gamma_1/\gamma_2)) \end{aligned} \quad (4.21c)$$

$$\begin{aligned} \mathcal{C}_{S_2 I_{12}}^\cdot &= \frac{F}{n} \frac{d}{dt} \left( \frac{[S_2 I_{12}]}{[S_2][I_{12}]} \right) \rightarrow \\ &\sigma + \mathcal{C}_{S_2 I_{11}} \gamma_2 - \mathcal{C}_{S_2 I_{12}} (\sigma + \gamma_2 + \beta_{212}/n) \end{aligned} \quad (4.21d)$$

In Eqs. (4.21), letting  $\mathcal{C}_{S_i I_{jk}}^\cdot = 0$  gives four equations for four variables. Here we do not list the full equations for  $\mathcal{C}_{S_i I_{jk}}^*$  because they are lengthy and not easily simplified.

As before, we analytically examine  $\mathcal{C}_{S_i I_{jk}}^*$  in two limiting cases and numerically examine them for other cases.

For instantaneous partnerships, we replace  $\sigma$  and  $\rho$  with  $\epsilon\sigma$  and  $\epsilon\rho$ . Taking  $\epsilon$  to infinity gives

$$\lim_{\epsilon \rightarrow \infty} \mathcal{C}_{S_i I_{jk}} = 1. \quad (4.22)$$

For fixed partnerships, we take  $\epsilon$  to zero. In this case,  $\mathcal{C}_{S_i I_{jk}}^*$  is again given as a lengthy equation and thus we only show  $\mathcal{C}_{S_1 I_{21}}^*$  as an example.

$$\lim_{\epsilon \rightarrow 0} \mathcal{C}_{S_1 I_{21}} = X/Y, \quad (4.23)$$

where

$$\begin{aligned}
X &= n^4(\beta_{121}\beta_{211}\gamma_2^2 + \beta_{122}\beta_{211}\gamma_1\gamma_2 + \beta_{121}\beta_{212}\gamma_1\gamma_2 + \beta_{122}\beta_{212}\gamma_1^2) \\
&+ n^3(\beta_{121}\beta_{122}\beta_{211}\gamma_2 + \beta_{121}\beta_{211}\beta_{211}\gamma_2 + \beta_{122}\beta_{211}\beta_{212}\gamma_1 + \beta_{121}\beta_{122}\beta_{212}\gamma_1) \\
&+ n^2(-\beta_{121}\beta_{211}\gamma_2^2 + \beta_{121}\beta_{122}\beta_{211}\beta_{212}) \\
&- n(\beta_{121}\beta_{122}\beta_{211}\gamma_2 + \beta_{121}\beta_{211}\beta_{212}\gamma_2) - \beta_{121}\beta_{122}\beta_{211}\beta_{212}
\end{aligned}$$

and

$$Y = n(n^2(\beta_{211}\gamma_2 + \beta_{212}\gamma_1) + n(\beta_{121}\gamma_2 + \beta_{122} + \beta_{212}) + \beta_{121}\beta_{212})(n(\beta_{121}\gamma_2 + \beta_{122}\gamma_1) + \beta_{121}\beta_{122}).$$

Again, letting  $\beta_{211} = \beta_{121}$  and  $\beta_{212} = \beta_{122}$  gives

$$\lim_{\epsilon \rightarrow 0} C_{S_1 I_{21}}^* = 1 - \frac{1}{n} \frac{\beta_{ij1}\beta_{ij2}/n + \beta_{ij1}\gamma_2}{\beta_{ij1}\beta_{ij2}/n + \beta_{ij1}\gamma_2 + \beta_{ij2}\gamma_1}, \quad (4.24)$$

which is the same as in the homosexual population case in Chapter 3.

#### 4.4.3 $\mathcal{R}_0$ and the fractional contribution to $\mathcal{R}_0$ of PHI between the extremes of instantaneous and fixed partnerships

In this section, we numerically examine  $\mathcal{R}_0$  and the fractional contribution to  $\mathcal{R}_0$  of PHI between the extremes of instantaneous and fixed partnerships. We vary partnership duration, average number of partners, and ratio of transmission rates (receptive to insertive sex acts). As for the ratio of transmission rates, we set  $\beta_{21k} = r\beta_{12k}$  for  $k = 1, 2$  and  $r = 1, 2, \dots, 10$  while keeping the sum of  $\beta_{21k}$  and  $\beta_{12k}$  constant.

As seen in Fig. 4.6,  $\mathcal{R}_0$  increases with increasing average number of partners, with decreasing partnership duration, and with decreasing difference in transmission rates between receptive and insertive sex acts.

As seen in Fig. 4.7, fractional contribution to  $\mathcal{R}_0$  of PHI initially drops, but rises with increasing partnership duration. It is slightly smaller for higher difference in transmission rates between insertive and receptive sex acts. And this is increasingly so with increasing partnership duration.

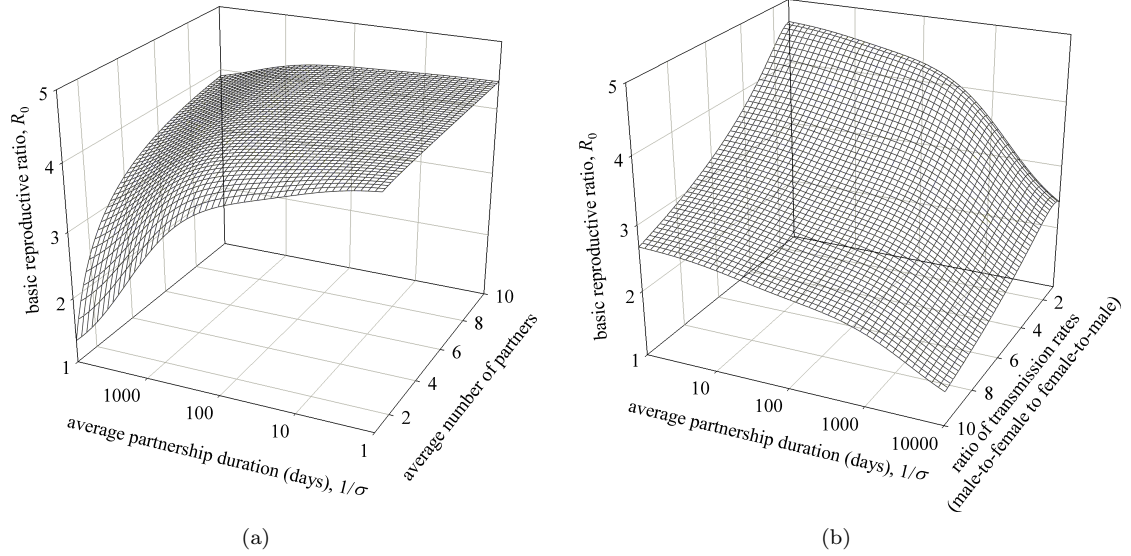


Figure 4.6:  $\mathcal{R}_0$  across partnership duration, average number of partners, and ratio of transmission rates (male-to-female to female-to-male).  $\beta_{121} + \beta_{211} = 0.072, \beta_{122} + \beta_{212} = 0.00168$ . In (a), transmission rate is two times higher in receptive (male-to-female) than insertive (female-to-male) sex (i.e.,  $\beta_{21k} = 2\beta_{12k}$ ). In (b), average number of partners is two (i.e.,  $\rho/2/\sigma = 2$ ).

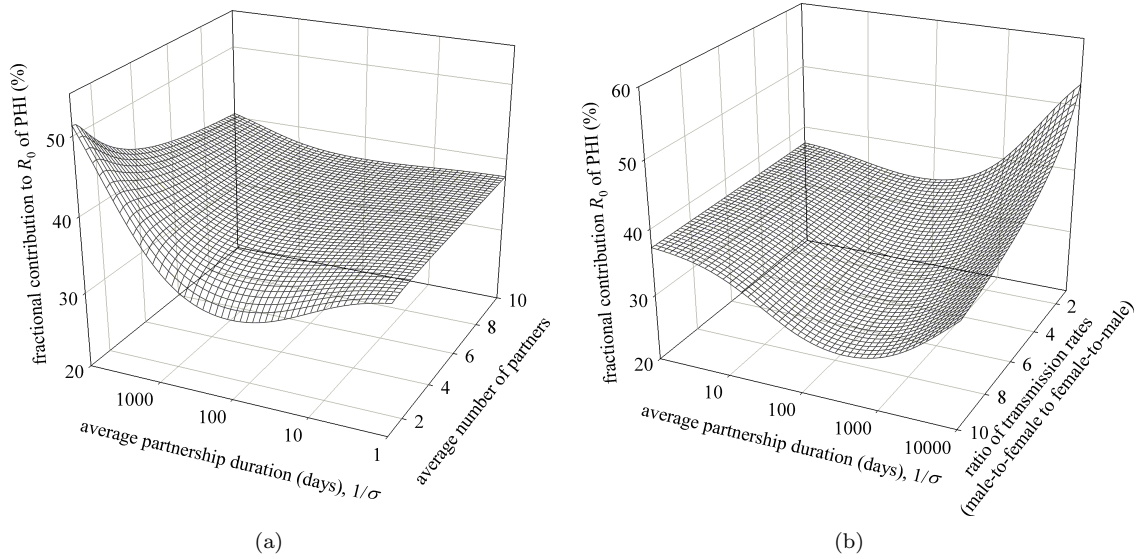


Figure 4.7: Fractional contribution to  $\mathcal{R}_0$  of PHI (%) across partnership duration, average number of partners, and ratio of transmission rates (male-to-female to female-to-male).  $\beta_{121} + \beta_{211} = 0.072, \beta_{122} + \beta_{212} = 0.00168$ . In (a), transmission rate is two times higher in receptive than insertive sex (i.e.,  $\beta_{21k} = 2\beta_{12k}$ ). In (b), average number of partners is two (i.e.,  $\rho/2/\sigma = 2$ ).

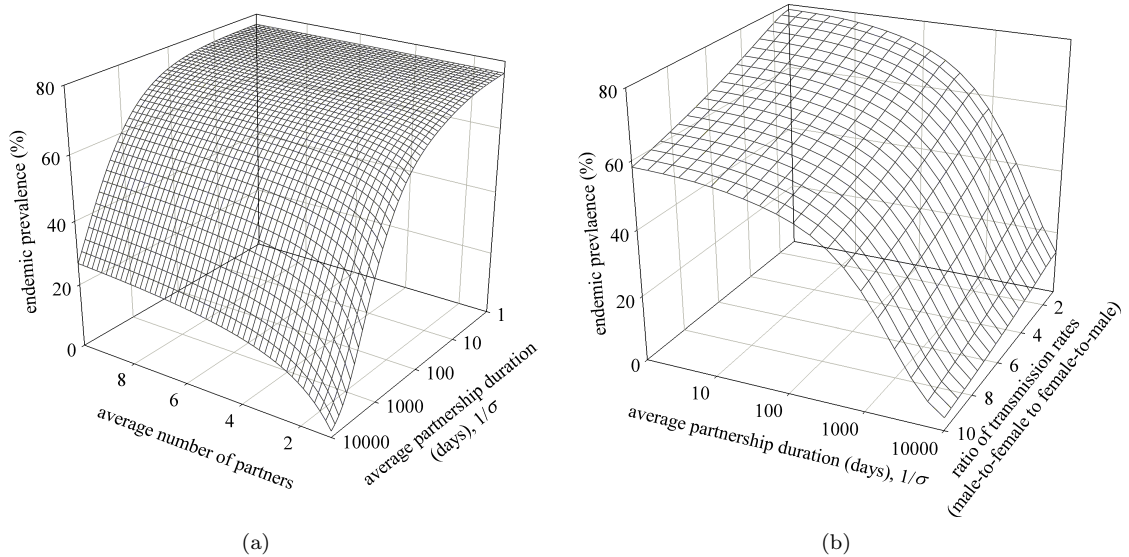


Figure 4.8: Endemic prevalence (%) across partnership duration, average number of partners, and ratio of transmission rates (male-to-female to female-to-male).  $\beta_{121} + \beta_{211} = 0.072, \beta_{122} + \beta_{212} = 0.00168$ . In (a), transmission rate is two times higher in receptive (i.e., male-to-female) than insertive (i.e., female-to-male) sex (i.e.,  $\beta_{21k} = 2\beta_{12k}$ ). In (b), average number of partners is two (i.e.,  $\rho/2/\sigma = 2$ ).

#### 4.4.4 Endemic prevalence and the fraction of transmissions from PHI at endemic phase

We also examined endemic prevalence and the fraction of transmissions from PHI at endemic phase. As Fig. 4.8a illustrates, endemic prevalence monotonically decreases with increasing partnership duration and decreasing average number of partners. Fig. 4.8b shows that endemic prevalence is higher when the ratio in transmission rates between insertive and receptive sex acts is smaller.

In Figs 4.9a, the fraction of transmissions from PHI at endemic phase initially drops, but rises again as partnership duration increases. In Fig. 4.9b, we see that the fraction of transmissions from PHI rarely changes with the difference in transmission rates between receptive and insertive sex acts. This is different from the change in the fractional contribution to  $\mathcal{R}_0$  of PHI, as shown in Fig. 4.7b. This seems to arise because the increase in endemic prevalence with decreasing difference in transmission

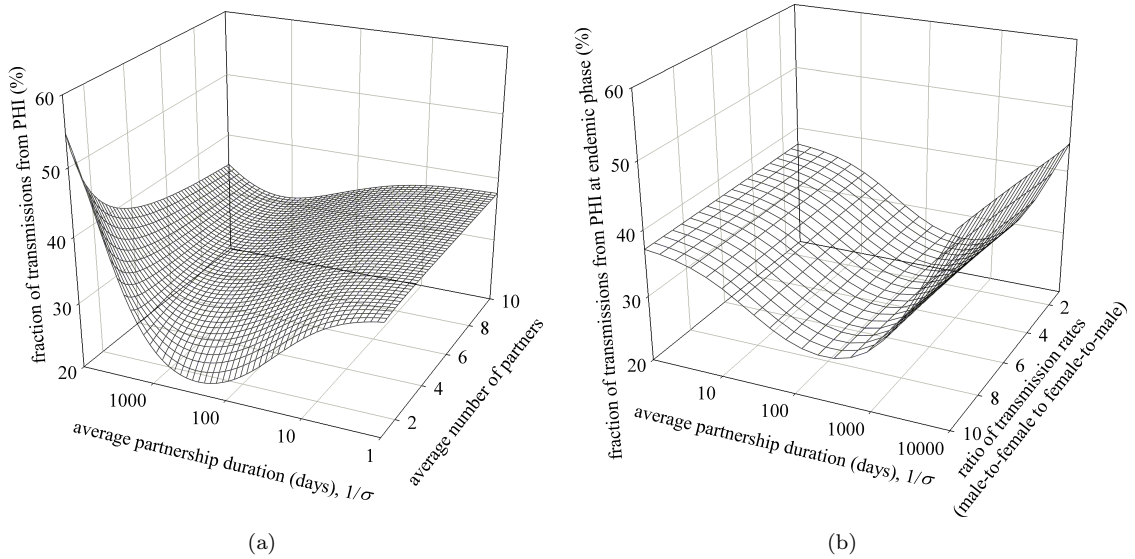


Figure 4.9: The fraction of transmissions from PHI (%) across partnership duration, average number of partners, and ratio of transmission rates (male-to-female to female-to-male).  $\beta_{121} + \beta_{211} = 0.072$ ,  $\beta_{122} + \beta_{212} = 0.00168$ . In (a), transmission rate is two times higher in receptive (i.e., male-to-female) than insertive (i.e., female-to-male) sex (i.e.,  $\beta_{21k} = 2\beta_{12k}$ ). In (b), average number of partners is two (i.e.,  $\rho/2/\sigma = 2$ )

rates between insertive and receptive sex acts counteracts the increase in the fraction of transmissions from PHI.

#### 4.4.5 Endemic prevalence and the fraction of transmissions from PHI at endemic phase with background removal

Finally, we examined whether including background removal changes patterns of endemic prevalence and the fraction of transmissions from PHI at endemic phase. As Figs. 4.10a and 4.10b, including background removal rate decreases endemic prevalence, compared with the case without background removal. This is expected since including background removal reduces transmission potential. However, overall patterns are similar. Endemic prevalence increases with increasing average number of partners, decreasing partnership duration, and decreasing difference in transmission rates between insertive and receptive sex acts.

As Figs. 4.11a and 4.11b illustrate, patterns of the fraction of transmissions from

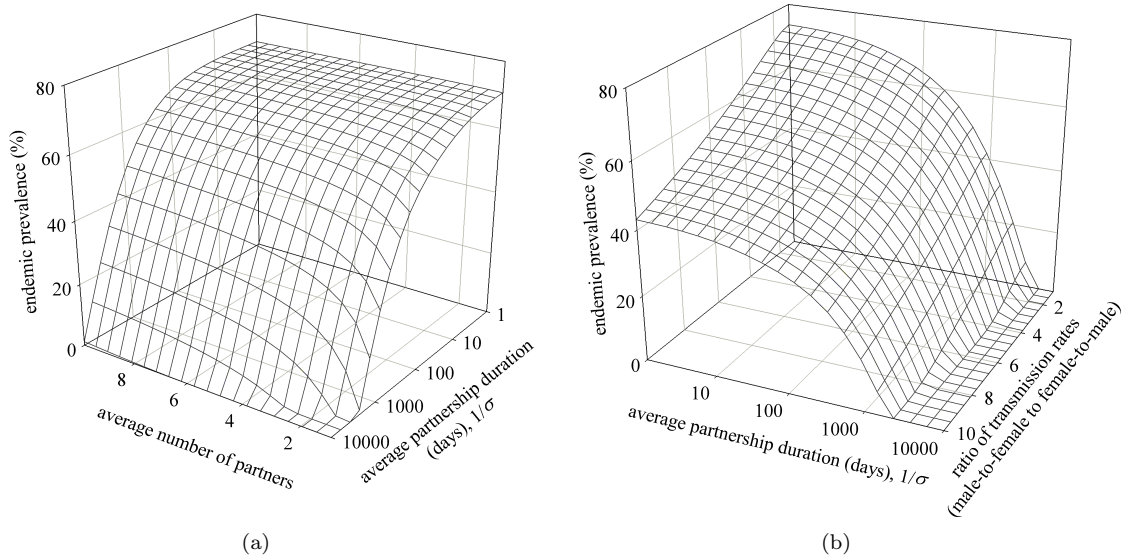


Figure 4.10: Endemic prevalence across partnership duration, average number of partners, and ratio of transmission rates (male-to-female to female-to-male) with background removal.  $\beta_{121} + \beta_{211} = 0.072$ ,  $\beta_{122} + \beta_{212} = 0.00168$ ,  $1/\mu = 9125$ . In (a), transmission rate is two times higher in receptive (i.e., male-to-female) than insertive (i.e., female-to-male) sex (i.e.,  $\beta_{21k} = 2\beta_{12k}$ ). In (b), average number of partners is two (i.e.,  $\rho/2/\sigma = 2$ ).

PHI at endemic phase does not change by including background removal either. It initially drops, but rises again as partnership duration increases. It rarely changes by the difference in transmission rates between insertive and receptive sex acts.

#### 4.5 Discussion

We have shown that both  $\mathcal{R}_0$  and the fractional contribution to  $\mathcal{R}_0$  of PHI decrease as the difference in transmission rates between insertive and receptive sex acts increases. Since the change in the fractional contribution to  $\mathcal{R}_0$  of PHI is not seen under instantaneous partnerships, it seems important to model sexual role segregation in the context of dynamic sexual partnerships when examining the fraction of transmissions from PHI.

It is noteworthy that the fraction of transmissions from PHI at endemic phase has different patterns from the fractional contribution to  $\mathcal{R}_0$  of PHI. With decreasing dif-



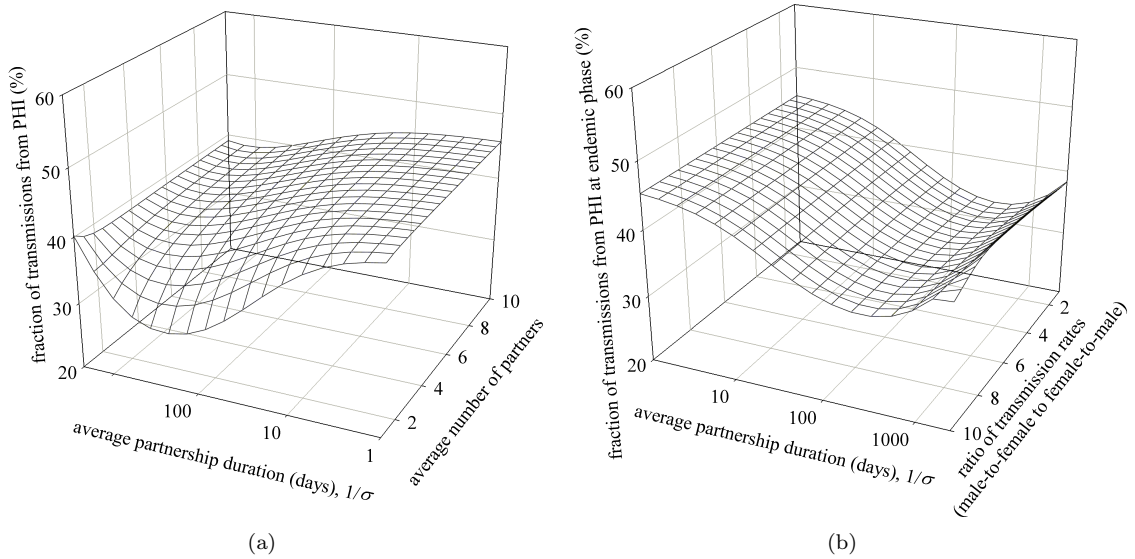


Figure 4.11: The fraction of transmissions from PHI (%) across partnership duration, average number of partners, and ratio of transmission rates (male-to-female to female-to-male) with background removal.  $\beta_{121} + \beta_{211} = 0.072$ ,  $\beta_{122} + \beta_{212} = 0.00168$ ,  $1/\mu = 9125$ . In (a), transmission rate is two times higher in receptive than insertive sex (i.e.,  $\beta_{21k} = 2\beta_{12k}$ ). In (b), average number of partners is two (i.e.,  $\rho/2/\sigma = 2$ ).

ference in transmission rates between insertive and receptive sex acts, the fractional contribution to  $\mathcal{R}_0$  of PHI increases whereas the fraction of transmissions from PHI at endemic phase remains more or less constant. It seems that this arises because the increase in endemic prevalence with decreasing difference in transmission rates between insertive and receptive sex acts counteracts the increase in the fraction of transmissions from PHI.

Our results means that modeling uniform sex acts could overestimate infection level and the fraction of transmissions from PHI at a given endemic prevalence. We have shown that in Chapters 2 & 3, partnerships lasting a few months to a few years can decrease both endemic prevalence and the fraction of transmissions from PHI. Sexual role segregation with different transmission rates for different roles can additionally decrease endemic prevalence and the fraction of transmissions from PHI.

## CHAPTER V

### High-Risk Behaviors and HIV Transmissions by Stage

#### 5.1 Abstract

**Objective:** We sought to understand how risk behavior change influences endemic prevalence of human immunodeficiency virus (HIV) infection and the fraction of transmissions from primary HIV infection (PHI) in the context of dynamic partnerships.

**Methods:** We constructed a stochastic individual-based model of HIV transmission in a population where sexual partnerships are formed and broken. At any point in time, there are two subpopulations across which individuals have different risks. Over time individuals can move between the subpopulations.

**Results:** Risk behavior change increases population levels of HIV infection and the fraction of transmissions from PHI, compared with when individuals stay in one risk phase for their entire sexually-active period. For example, if individuals stay in high-risk phase for two years and nine times longer in low-risk phase, endemic prevalence increases up to about 22% while it remains around 3% without risk behavior change. Under the same conditions, the fraction of transmissions from PHI at endemic equilibrium increases up to about 35% whereas it remains around 32% without risk behavior change. The fraction, however, remains lower than the frac-

tion of transmission potential from PHI ( $\sim 38\%$ ) under all parameter choices. Risk behavior change causes individuals infected by individuals with PHI to produce more than one secondary cases. By contrast, it causes individuals infected by individuals with later infections to produce fewer than one secondary case on average. Thus, a control program can be more effective when it eliminates transmissions from PHI than from later stages.

**Conclusions:** Risk behavior change increases population levels of HIV infection and the fraction of transmissions from PHI. In the context of long-term partnerships, however, the fraction of transmissions from PHI can remain lower compared with its transmission potential.

## 5.2 Introduction

Various external factors such as population heterogeneity have a strong influence on the sexual transmission of human immunodeficiency virus (HIV). This means that at a given duration and infectivity, endemic prevalence of HIV infection varies by those external factors. Likewise, the fraction of new infections attributable to a particular stage of infection is influenced by those external factors [43, 44, 45, 74].

In HIV transmission, getting the fraction of new infections attributable to a particular stage of infection as well as overall population level of infection right can be important. Effectiveness of a HIV control program such as a vaccine that does not prevent infection, but still lowers the initial viremia during primary HIV infection (HIV) [60, 61] can vary significantly by the fraction of transmissions occurring during PHI. Likewise, antiretroviral therapy that may miss individuals who have PHI will have a different effectiveness depending on which stage of HIV infection is dominant.

In this paper, we examine the effects of two factors on endemic prevalence of HIV

infection and on the fraction of transmissions from PHI. One is sexual partnerships and the other risk behavior change. We showed that sexual partnerships that last for a few months to a few years can decrease endemic prevalence and the fraction of transmissions from PHI. On the other hand, under instantaneous partnerships, if individuals move between different risk phases, the fraction of transmissions from PHI [42, 75] as well as endemic prevalence [42] increases. That is, risk behavior change and long-lasting sexual partnerships have opposite effects on both endemic prevalence and the fraction of transmissions from PHI. In this paper, we examine how endemic prevalence and the fraction of transmissions from PHI vary when these two factors coexist.

We constructed a stochastic individual-based model of HIV transmission in a population where partnerships are formed and broken. In the population, there are always two subpopulations across which individuals have different risks. Individuals can move between the risk phases. In high-risk phase, individuals meet partners more often and form shorter-lived partnerships than in low-risk phase. We fix partnership duration and new partnering rate in low-risk phase, but vary them in high-risk phase. We seek to identify conditions and mechanisms that influence the fraction of transmissions from PHI and endemic prevalence.

Risk behavior change increases endemic prevalence and the fraction of transmissions from PHI. However, the fraction of transmissions from PHI was never above the fraction of transmission potential from PHI under all parameter choices. Mechanisms by which long-lasting partnerships decreases endemic prevalence and the fraction of transmissions from PHI are different from those by which risk behavior change increases them.

## 5.3 Methods

### 5.3.1 Natural history of HIV infection

The natural history of HIV infection is modeled with three periods, each having different transmission probability. First, we model a brief period of high transmission probability associated with primary HIV infection (PHI) with an average duration of 49 days. Then a long period of low stable transmission probabilities lasting on average 7 years is modeled. Finally, a period averaging 1 year during late infection with higher transmission probability is modeled. We call these three periods PHI, asymptomatic stage and late stage, respectively. We ignore the incubation period before PHI because sensitivity analyses indicate that it does not qualitatively change results. We often use the term post-PHI stage to refer to both asymptomatic and late stages. Waiting time in each stage of infection follows an exponential distribution with given means.

### 5.3.2 Compartmental flows for the model analyzed

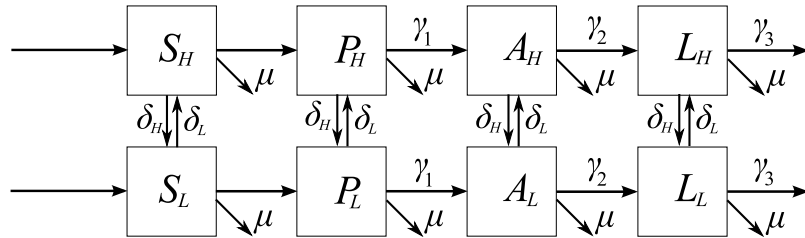


Figure 5.1: Compartmental flows for the model analyzed.  $S$ ,  $P$ ,  $A$ , and  $L$  represent infection categories: susceptible, primary HIV infection, asymptomatic, and the late stage of infection, respectively. Subscripts indicate the risk phase of individuals with  $L$  and  $H$  meaning low- and high-risk phase, respectively. The angled arrows represent removal from the sexually active population. The left hand horizontal arrows represent susceptible individuals entering the sexually active population in high or low risk phase. The other horizontal arrows represent infection and stage progression with the final arrow being death from AIDS. The vertical arrows represent that individuals make transitions between two risk phases.

Fig. 5.1 shows compartmental flows for the model. Individuals can be in one of eight compartments: four infection categories (susceptible, PHI, asymptomatic, and

late) and two risk phases (low and high). We can further divide compartments by partnership status. For simplicity, however, we present a diagram without partnership status. Susceptible individuals are continuously recruited to the population in either low- or high-risk phase so that the expected population size in each risk phase remains constant without death from AIDS. Individuals leave the population (i.e., become sexually inactive) at a constant probability regardless of risk phase or infection category.

### 5.3.3 Partnership dynamics

Two parameters—partnership formation probability,  $\rho$ , and dissolution probability,  $\sigma$ —mainly influence partnership dynamics.  $\rho$  and  $\sigma$  can vary by risk phase— $\rho_H, \rho_L, \sigma_H$ , and  $\sigma_L$ —but are independent of infection category.

A partnership is formed between two individuals chosen uniformly at random from the same risk phase. The partnership formation probability can vary by partnership status, which is represented by the parameter  $\theta \in [0, 1]$  [49].  $\theta$  indicates the ratio of partnership formation probabilities comparing two individuals of which at least one is not single to two single individuals. That is, if the partnership formation probability is  $\rho$  between two single individuals, then it is  $\rho\theta$  for two individuals of which at least one is not single. If  $\theta = 1$ , the current partnership status of an individual does not affect the probability of gaining a new partner or losing an existing one. That is, if  $\theta = 1$ , the distribution of the number of partners per person follows a Poisson distribution in the limit of large population size. If  $\theta = 0$ , no individual may have more than one partner. In short,  $\theta$  provides a transition from monogamy to Poisson random partnerships.

Despite variable  $\theta$ 's, we keep the expected number of partnerships formed in the overall population constant, which is done as follows. Suppose partnerships are

formed for  $N_L$  times with probability  $\rho_L$  with a certain value of  $\theta_L$ . For  $N_L$  times we repeat following steps:

1. Use the probability  $\rho_L$  to determine whether a new partnership is to be formed.
2. If a new partnership is to be formed, then two individuals are chosen uniformly at random.
  - (a) If two individuals are both single, then they will become partners.
  - (b) If at least one of them is not single, then they will become partners with probability  $\theta_L$ .
3. If no partnership is formed, repeat the second step until a new partnership is formed.

In doing so, the expected number of new partnerships is  $\rho_L N_L$  regardless of  $\theta_L$  values.

At each time step, partnerships dissolve with probability  $\sigma_H$  or  $\sigma_L$ . As mentioned earlier, partnerships are formed between individuals from the same risk phase and thus two members in a partnership are in the same risk phase when partnerships are formed. However, individuals change their risk over time and so risk phases of two individuals in a partnership can be different. In this case the dissolution probability of that partnership is solely determined by the risk phase where the partnership was originally formed.

There are two more ways whereby partnerships can dissolve: when one's partner dies of AIDS or leaves the sexually active population.

#### **5.3.4 Average number of partners**

Average number of partners per person can be computed with partnership formation and dissolution probabilities and the probability individuals become sexually

inactive. For example, in high-risk phase, without both death from AIDS and risk behavior change, the following relationship holds at equilibrium:

$$\rho_H N_H / 2 = (2\mu + \sigma_H) P_H, \quad (5.1)$$

where  $N_H$  and  $P_H$  indicate the number of individuals and partnerships in high-risk phase at equilibrium, respectively. From this relationship, average number of partners per person at equilibrium in high-risk phase,  $n_H$ , is given as:

$$n_H = 2P_H / N_H = \rho_H / (2\mu + \sigma_H) \quad (5.2)$$

Once death from AIDS occurs, the above relationship does not hold because individuals who die of AIDS dissolve their partnerships. Similarly, risk behavior change also changes the observed number of partnerships in each risk phase because individuals who flow in and those flow out of a risk phase will have different number of partnerships. Furthermore, risk behavior change generates partnerships across the risk phases.

### 5.3.5 Probability of infection

If a susceptible individual has  $n$  infected partners on a certain day, then the probability the susceptible individual becomes infected on that day is

$$1 - \prod_{k=1}^n (1 - \omega_k)^{X_k}. \quad (5.3)$$

Here  $\omega_k$  is the transmission probability per sex act of the  $k^{th}$  infected partner and is determined by the infected partner's stage of infection (i.e.,  $\omega_k = \lambda_1, \lambda_2, \lambda_3$ ).  $X_k$  is the frequency of sex acts per day in the partnership between the susceptible and the  $k^{th}$  infected partner. This is a Poisson random variable with parameter  $c$ , which is the mean frequency of sex acts per partnership per day.



### 5.3.6 Model Simulation

Model parameters appear in Table 5.1. We start off with entirely susceptible populations of sizes  $N_H(0)$  and  $N_L(0)$  in high and low-risk phase, respectively. After partnership dynamics reach equilibrium, we randomly choose 1% of the population in each risk phase and set them as initially infecteds with PHI. After infection dynamics reach equilibrium, variables of interest are measured. For example, to get an estimate for endemic prevalence for a particular set of parameter choices, endemic prevalence is calculated as an average over 40,000 time steps after 60,000 time steps of equilibration period. Then, we calculate an average of time-averaged endemic prevalence from ten simulation runs.

The following events occur at each time step:

1. Individuals leave the sexually active population with probability  $\mu$ .
2. A new susceptible is recruited with probability  $\mu$  to high-risk phase. This is repeated for  $N_H(0)$  times.
3. A new susceptible is recruited with probability  $\mu$  to low-risk phase. This is repeated for  $N_L(0)$  times.
4. Individuals move from high- to low-risk phase with probability  $\delta_H$ . The reverse transition occurs with probability  $\delta_L = \delta_H f / (1 - f)$ .
5. Partnerships are formed for  $N_L(t)/2$  and  $N_H(t)/2$  times with average probability  $\rho_L$  and  $\rho_H$  in low- and high-risk phases, respectively.  $N_L(t)$  and  $N_H(t)$  indicate population size of low- and high-risk phases at current time step, respectively. Concurrency of partnerships can be varied using  $\theta_L$  and  $\theta_H$  in low- and high-risk phases, respectively.
6. Partnerships formed in low-risk phase dissolve with probability  $\sigma_L$  and those

Table 5.1: Model parameters. Probabilities are defined per day.

Symbol	Values explored	Description
$N_k(0)$	$\{N_H(0), N_L(0)\}$ $= \{1111, 10000\}$	Initial population size in risk phase $k$ for $k = L, H$ ( $L$ =low-, $H$ =high-risk phase).
$f$	0.1	Fraction of individuals in the high risk phase before HIV is introduced.
$c$	0.5	Average number of sex acts per partnership per day.
$\lambda_i$	$\{\lambda_1, \lambda_2, \lambda_3\} =$ $\{0.03604, 0.00084, 0.00421\}$	Transmission probability per act during stage $i$ for $i = 1, 2, 3$ (1=PHI, 2=asymptomatic stage, 3=late stage).
$\gamma_i$	$\{\gamma_1, \gamma_2, \gamma_3\}$ $= \{1/49, 1/2555, 1/365\}$	Progression probability from state $i$ to the next for $i = 1, 2, 3$ (1=PHI, 2=asymptomatic stage, 3=late stage).
$\sigma_k$	$\sigma_L = 0.005,$ $\sigma_H \in [0.005, 0.1]$	Dissolution probability of a partnership formed in risk phase $k$ for $k = L, H$ ( $L$ =low-, $H$ =high-risk phase).
$\rho_k$	$\rho_L = 0.0019,$ $\rho_H \in [0.0036, 0.073]$	Partnership formation probability in risk phase $k$ for $k = L, H$ ( $L$ =low- and $H$ =high-risk phase).
$\mu$	1/9125	Probability an individual leaves the sexually active population.
$\theta_k$	$\theta_L = 0.3, 1$ $\theta_H = 1$	The ratio of partnership formation probabilities comparing a partnership between two individuals of whom at least one is not single to a partnership between two single individuals in risk phase $k$ for $k = L, H$ ( $L$ =low-, $H$ =high-risk phase).
$\delta_H$	0, 0.011, 0.00137	Probability an individual moves from high- to low-risk phase.
$\delta_L$	$\delta_H f / (1 - f)$	Probability an individual moves from low- to high-risk phase.

formed in high-risk phase dissolve with probability  $\sigma_H$ .

7. Infection transmission occurs in a partnership consisting of susceptible and infected partners.

8. Infected individuals progress from stage  $i$  to the next with probability  $\gamma_i$ .

After partnership dynamics come to equilibrium through events from 1 to 6, we add events 7 and 8.

### 5.3.7 Simulation scenarios

Risk behavior change are expressed in terms of time that individuals spend in high-risk phase. We examine three scenarios—no risk behavior change (i.e.,  $\delta_H = 0$ ),

3 months (i.e.,  $\delta_H = 0.011$ ) and 2 years (i.e.,  $\delta_H = 0.00137$ ) in high-risk phase. Without risk behavior change (i.e.,  $\delta_H = 0$ ), one tenth of the population remain in high-risk phase and the rest in low-risk phase in the absence of deaths from AIDS. With risk behavior change, individuals stay in high-risk phase for the assigned time on average and stay in low-risk phase nine times longer. Therefore, regardless of risk behavior change, one tenth of the population is in high-risk phase at any point in time in the absence of deaths from AIDS.

Durations of 3 months and 2 years in high-risk phase were chosen based on HIV sexual risk behavioral data from a cohort of gay men in Amsterdam [76]. Also, in our study [42], we found that endemic prevalence of HIV infection and the fraction of transmissions from PHI at endemic phase increase significantly if individuals spend a few months to a few years in high-risk phase.

In high-risk phase, individuals meet partners more often, but their partnerships are shorter-lived (even if members move to low-risk phase) than in low-risk phase. For low-risk phase, we fix the average duration and average formation rate of partnerships at about 200 days (i.e.,  $\sigma_L = 0.005$ ) and at 1 per about 500 days (i.e.,  $\rho_L = 0.0019$ ), respectively. For high-risk phase, we vary average duration and formation rate of partnerships from about 10 days to 200 days (i.e.,  $\sigma_H \in [0.005, 0.1]$ ) and from 1 per about 280 days to 1 per 14 days (i.e.,  $\rho_H \in [0.0036, 0.073]$ ), respectively. While varying partnership formation and dissolution probabilities in high-risk phase, we keep the average number of partners in high-risk phase without risk behavior change and without death from AIDS,  $n_H = \rho_H / (2\mu + \sigma_H)$ , constant.

In the analyses followed, we present the difference in partnership formation and dissolution probabilities between the risk phases as the ratio of partnership formation probability per day in high- to low-risk phase (i.e.,  $\rho_H / \rho_L$ ).

Across parameter choices, we examine endemic prevalence and the fraction of transmissions from PHI at endemic phase in low-risk phase, high-risk phase, and the overall population.

### 5.3.8 Control programs

HIV transmission control programs we model are abstract. Control programs are applied either on PHI or a post-PHI stage. For control programs applied on PHI, we model a decrease in transmission probability only during PHI and not during the post-PHI. This effect might arise from a vaccine that fails to prevent infection but still lowers the initial peak viral level [60, 61, 77, 78]. Similarly, for control programs applied on post-PHI we model a decrease in transmission probability during post-PHI while leaving the transmission probability during PHI intact. This could arise from diagnosis and treatment of cases that have already passed their PHI. Since our goal is to clarify transmission effects in different stages of infection, we do not consider various realistic control program aspects that would cause deviations from uniform control throughout PHI or post-PHI periods.

To reduce roughly the same transmissions from either PHI or post-PHI, we use the following logic. The fraction of transmission probability reduced from post-PHI is given as  $\alpha\zeta_{PHI}/(1-\zeta_{PHI})$ , where  $\alpha$  is the fraction of transmission probability reduced from PHI and  $\zeta_{PHI}$  is the fraction of transmissions from PHI in the overall population without a control program. That is, if the transmission probability during PHI under a control program is  $\lambda_1(1-\alpha)$ , then  $\lambda_2(1-\alpha\zeta_{PHI}/(1-\zeta_{PHI}))$  is the transmission probability during asymptomatic stage. Similarly,  $\lambda_3(1-\alpha\zeta_{PHI}/(1-\zeta_{PHI}))$  is the transmission probability during late stage of infection under the control program. We vary  $\alpha$  from zero to one. Under all parameter choices we have explored,  $\zeta_{PHI}$  is always smaller than 0.5 and so  $\zeta_{PHI}/(1-\zeta_{PHI})$  is always less than 1. This means

that  $\lambda_2$  and  $\lambda_3$  never go down to zero even when  $\lambda_1$  does.

## 5.4 Results

### 5.4.1 Effects of risk behavior change on endemic prevalence

As seen in Fig. 5.2a, risk behavior change of individuals increases endemic prevalence in the overall population. As we increase the difference in the rate of partner change between the risk phases, the increase in endemic prevalence by risk behavior change becomes larger. As Figs. 5.2b and 5.2c illustrate, infection levels decrease in high-risk phase and increase in low-risk phase with risk behavior change.

Saturation of infection in the “core” group was once demonstrated as a reason why the endemic prevalence of gonorrhea, which doesn’t confer immunity, is sustained at a low level in the overall population [79]. That is, since the endemic prevalence is high in the “core” group, many sex acts occur between already infected individuals and thus are not used to produce new infections. Risk behavior change increases the endemic prevalence by replenishing susceptibles to high-risk phase from low-risk phase (thereby canceling saturation of infection in high risk phase) and also spreading infection from high- to low-risk phase. Replenishing of susceptibles from low- to high-risk phase and spreading of infection from high- to low-risk phase are indirectly shown in Figs. 5.2b and 5.2c where endemic prevalence is lowered in high-risk phase and is increased low-risk phase.

### 5.4.2 Effects of risk behavior change on the fraction of transmissions from PHI

Fig. 5.3a shows the fraction of transmissions from PHI in the overall population is increased by risk behavior change. Even without risk behavior change, increasing the rate of partner change in high-risk phase increases the fraction of transmissions from PHI in high-risk phase and thus in the overall population. The increase is, however,

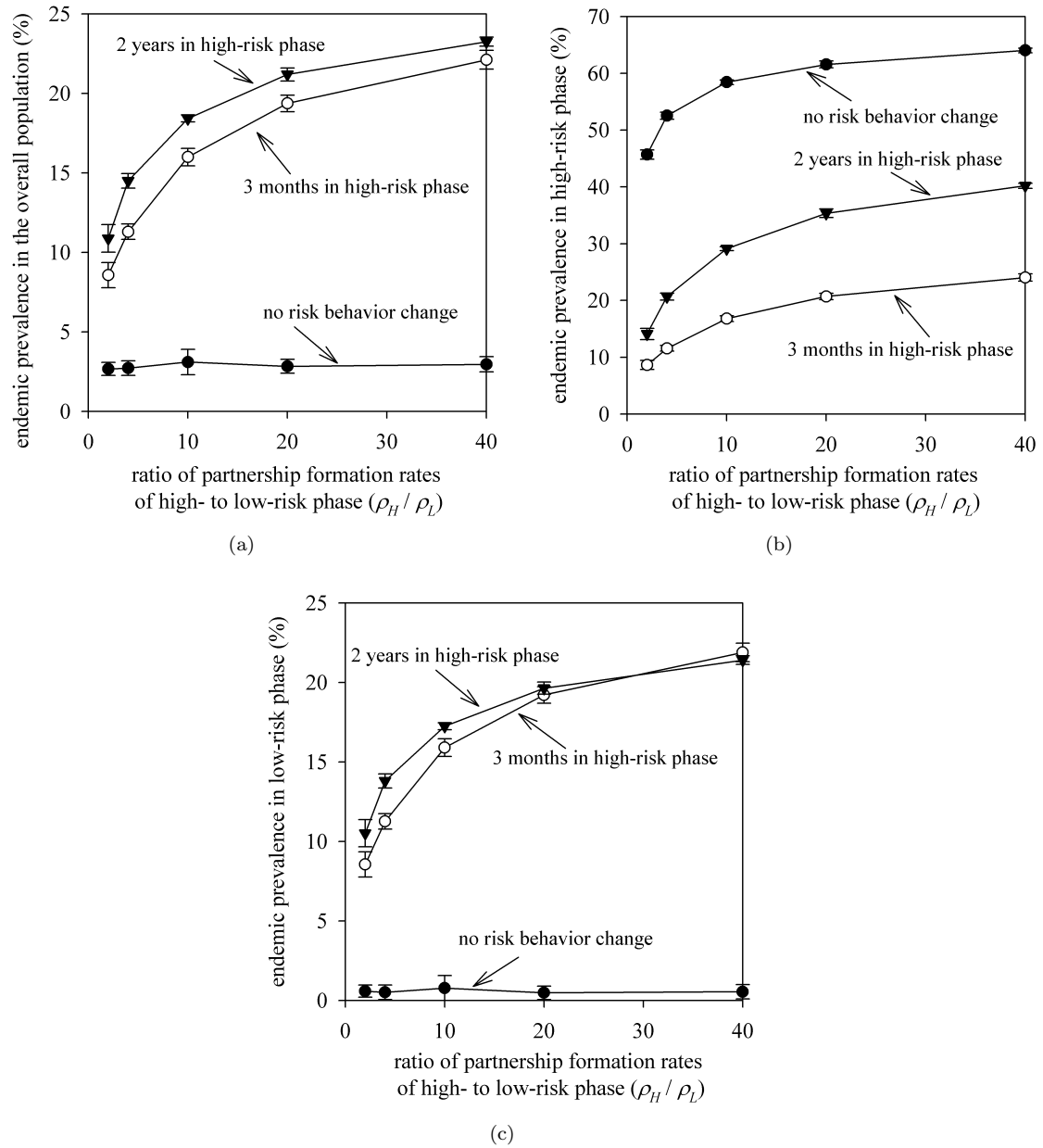


Figure 5.2: Endemic prevalence (%) at three different rates of risk behavior change,  $\delta_H$ , as the rate of partner change in high-risk phase is varied. (a), (b) and (c) show endemic prevalence in the overall population, in high-risk phase, and in low-risk phase, respectively. Each data point is the mean from ten simulation runs and error bars show one standard deviation.

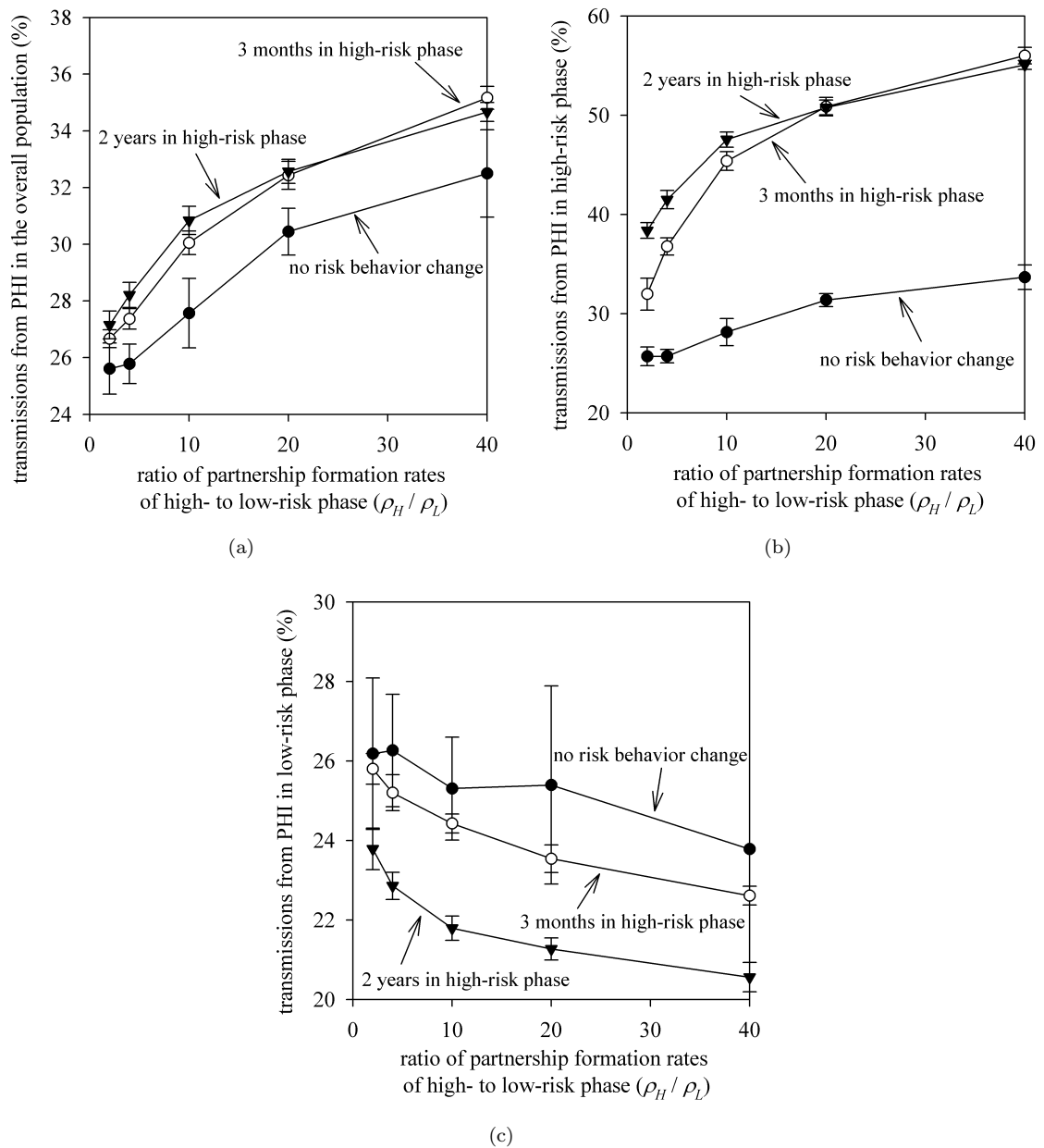


Figure 5.3: Fraction of transmissions from PHI (%) at three different rates of risk behavior change,  $\delta_H$ , as the rate of partner change in high-risk phase,  $\rho_H$ , is varied. (a), (b) and (c) show fraction of transmissions from PHI in the overall population, in high-risk phase, and in low-risk phase, respectively. Each data point is the mean from ten simulation runs and error bars show one standard deviation. In (c), the fraction of transmissions from PHI at  $\delta_H = 0$  (filled circle) has large standard deviations compared with the others. This is because the number of infected individuals that were used to calculate the fraction of transmissions from PHI is small at  $\delta_H = 0$ . This is, in turn, because endemic prevalence is low ( $\sim 1\%$ ) at  $\delta_H = 0$ , as seen in Fig 5.2c.

augmented by risk behavior change. In Figs. 5.3b and 5.3c, we see the fraction of transmissions from PHI increases in high-risk phase, but decreases in low-risk phase in the presence of risk behavior change.

We previously showed that sexual partnerships lasting for a few months to a few years decrease transmissions more during PHI than during post-PHI both in homosexual and in heterosexual populations. Thus, it is natural that increasing the rate of partner change in high-risk phase increases the fraction of transmissions from PHI in high-risk phase. This, in turn, increases the fraction of transmissions from PHI in the overall population given the fraction of transmissions from PHI in low-risk phase remains roughly constant.

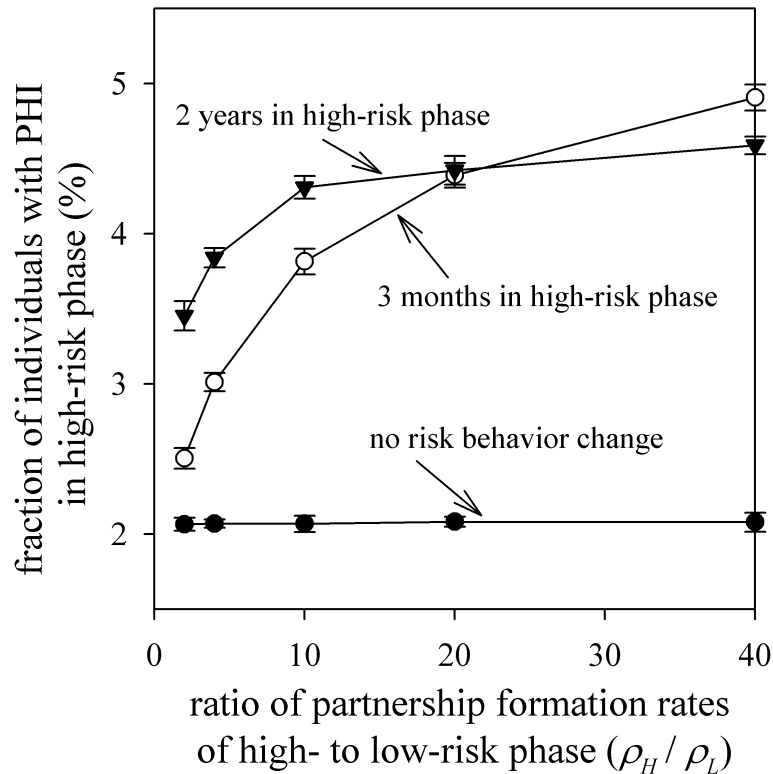


Figure 5.4: Fraction of individuals with PHI at three different rates of risk behavior change as the rate of partner change in high-risk phase is varied. Each data point is the mean from ten simulation runs and error bars show one standard deviation.

An additional increase in the fraction of transmissions from PHI by risk behavior



change occurs as follows. When there is risk behavior change, infected individuals with PHI are more likely to be in high-risk phase than in low-risk phase. This is seen in Fig. 5.4. Risk behavior change increases the fraction of individuals with PHI up to 5% compared with 2% when there is no risk behavior change. Since the fraction of transmissions from PHI is higher in high-risk phase than in low-risk phase even without risk behavior change, increasing the fraction of individuals with PHI in high-risk phase increases the fraction of transmissions from PHI in the overall population.

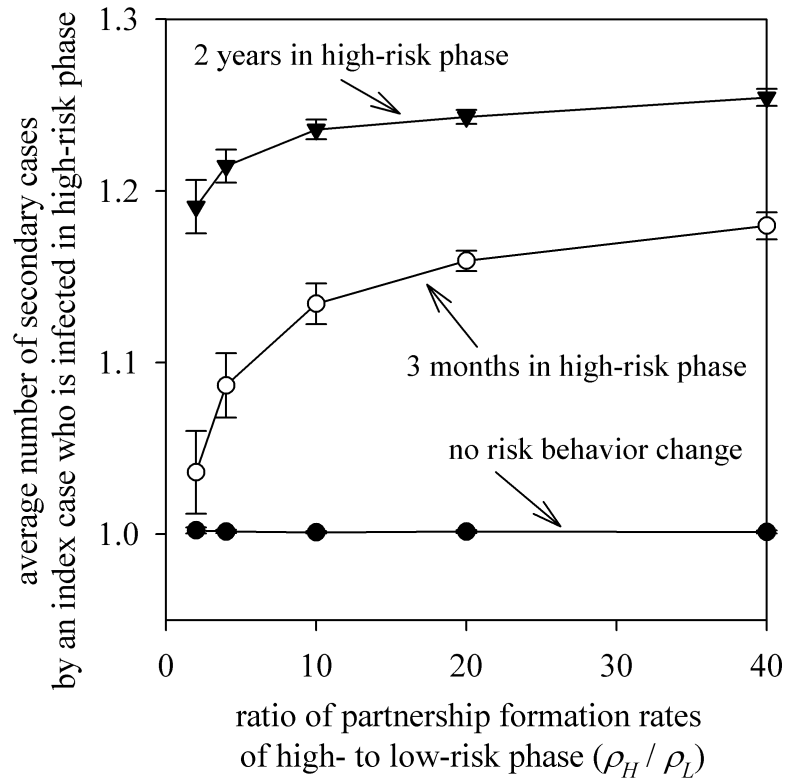


Figure 5.5: Average number of secondary cases by an index case who is infected in high-risk phase as the rate of partner change in high-risk is varied. Each data point is the mean from ten simulation runs and error bars show one standard deviation.

### 5.4.3 Effects of risk behavior change on the average number of secondary cases

As seen in Fig. 5.5, the average number of secondary cases at equilibrium increases above one given the index case is produced in high-risk phase and there is a risk

behavior change. It also increases with increasing difference in the rate of partner change between the risk phases. When there is no risk behavior change, the average number of secondary cases equals one at equilibrium regardless of the risk phases (only high-risk phase is shown in Fig. 5.5).

The increase in the average number of secondary cases by risk behavior change arises because an index case produced in high-risk phase is likely to spend more time in high-risk phase where they can generate more infections than in low-risk phase. By contrast, an index case produced in low-risk phase will spend more time in low-risk phase. Also, this difference is augmented because the course of HIV infection shows higher infectivity during PHI than during post-PHI. Thus, the index case produced in high-risk phase can spend their PHI in high-risk phase while moving to low-risk phase during post-PHI.

Similarly, in Fig. 5.6, the average number of secondary cases increases above one given the index case becomes infected by PHI individuals when there is risk behavior change. The average number of secondary cases increases as the difference in the rate of partner change between the risk phases increases.

The increase in the average number of secondary cases of those who become infected by PHI individuals is understood as follows. Since the fraction of transmissions from PHI is higher in high-risk phase than in low-risk phase, the index case that becomes infected by individuals with PHI are more likely to have become infected in high-risk phase than in low-risk phase. As we mentioned earlier, those who become infected in high-risk phase produce more than one secondary cases on average when there is a risk behavior change over time.

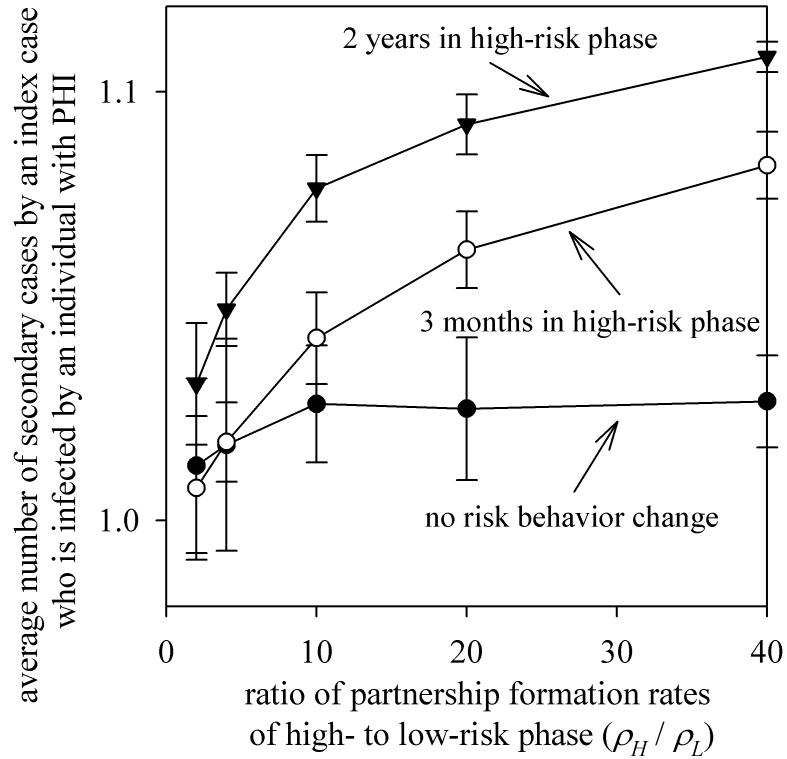


Figure 5.6: Average number of secondary cases by individuals with PHI as the rate of partner change in high-risk is varied. Each data point is the mean from ten simulation runs and error bars show one standard deviation.

#### 5.4.4 Effects of risk behavior change on control program effects

In the previous section, we showed that when the risk difference between the risk phases is high and when individuals change their risk behavior over time, the average number of secondary cases is larger than one given that the index case become infected by individuals with PHI. This may mean that a control program will be more effective at reducing infection levels when it eliminates transmissions from PHI than from post-PHI given the same number of transmission is eliminated from both PHI and post-PHI. On the other hand, if the rate of partner change is similar in both risk phases, the effectiveness of a control program might be similar regardless of whether it reduces transmissions from PHI or post-PHI.

As Fig. 5.7 illustrates, a control program becomes more effective at reducing

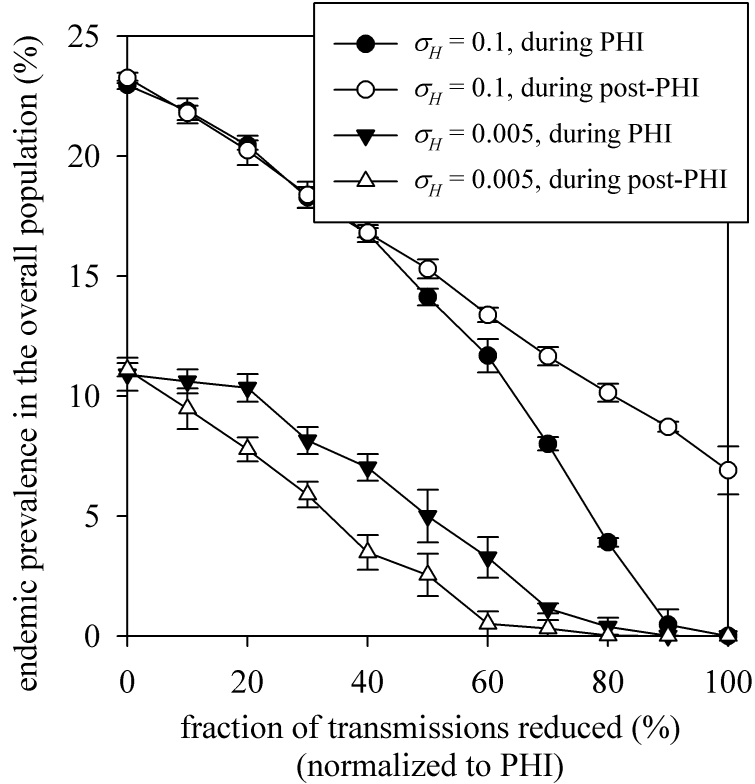


Figure 5.7: Effectiveness of reducing transmissions from PHI or post-PHI. Horizontal axis indicates the fraction of transmission probability reduced during PHI. In Section 5.3.8, we described how we reduce the comparable fraction of transmission probability during asymptomatic and the late stage. Each data point is the mean from ten simulation runs and error bars indicate one standard deviation. Endemic prevalence without a control program (i.e., leftmost points) is different for two scenarios because the rate of partner change in high-risk is different.

infection levels when it reduces transmissions from PHI than post-PHI if the rate of partner change in high-risk phase is higher than in low-risk phase ( $\sigma_H = 0.1$ ) and when there is a risk behavior change over time ( $\delta_H = 9\delta_L = 0.0014$ ). This is the same as we expected. On the other hand, reducing transmissions from PHI becomes less effective when the rate of partner change is alike both in low- and high-risk phases (i.e.,  $\sigma_H = 0.005$ ).

Decreased effectiveness of reducing transmissions from PHI at  $\sigma_H = 0.005$  is explained as follows. In a partnership between an infected with PHI and a susceptible, reducing transmission probability only during PHI may not keep the susceptible partner from becoming infected because the susceptible partner can still be infected

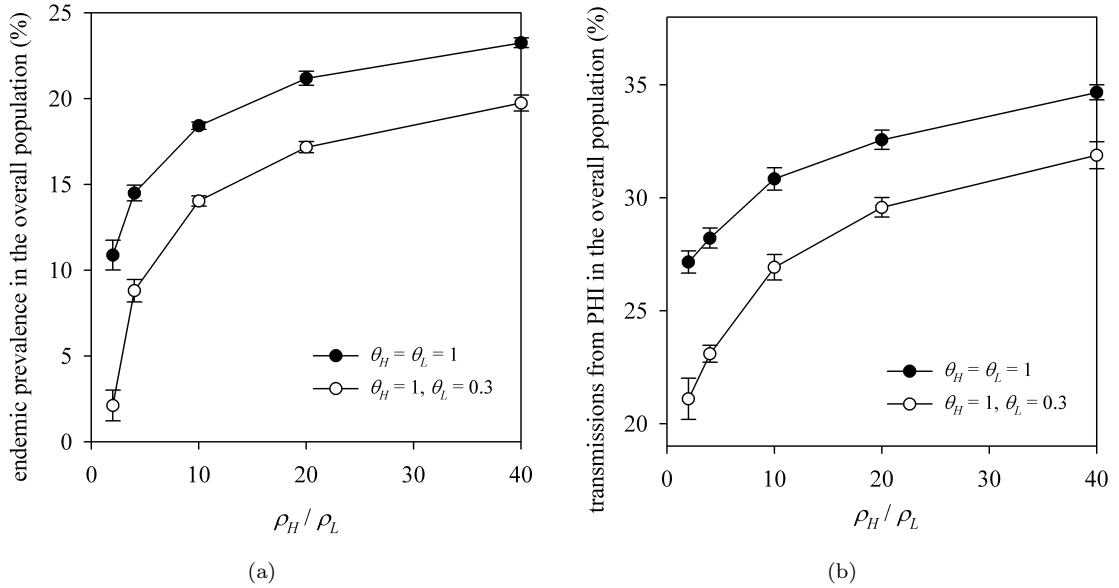


Figure 5.8: Endemic prevalence and the fraction of transmissions from PHI for different  $\theta$  as the rate of partner change in high-risk is varied. (a) shows endemic prevalence, (b) shows the fraction of transmissions from PHI. Each data point is the mean from ten simulation runs and error bars indicate one standard deviation.

if the partnership lasts after the infected partner have progressed to later stages of infection. Thus, a control program can be more effective at reducing infection level when it reduces transmission probability during post-PHI.

Lastly, we decreased partnership concurrency in low-risk phase while keeping partnerships in high-risk phase constant (i.e., random). As seen in Fig. 5.8, decreasing  $\theta_L$  decreases both endemic prevalence and the fraction of transmissions from PHI in the overall population.

## 5.5 Discussion

This study combines our recent findings regarding the role of PHI. First, we showed that sexual partnerships lasting for a few months to a few years decrease transmissions more during PHI than post-PHI in both homosexual and heterosexual populations. Also, when partnership concurrency is low, the decrease in the fraction

of transmissions from PHI at endemic phase becomes greater. On the other hand, we found that risk behavior change increases the fraction of transmissions from PHI in instantaneous partnerships [42].

If these factors coexist, we see the fraction of transmissions from PHI remains lower than we would expect from its transmission potential. Based on our parameter choices, the fraction of transmission potential during PHI is about 38%. Under all parameter choices we have explored, the fraction of transmissions from PHI remains lower than 38%.

It has been long since the saturation of infection in the “core” group was demonstrated as a reason why the endemic prevalence of gonorrhea, which does not confer immunity, is sustained at a low level in the overall population [79]. That is, since the endemic prevalence is already in the “core” group, many sex acts occur between already infected individuals and thus are not used to produce new infections. Risk behavior change increases endemic prevalence by replenishing susceptibles and thereby canceling saturation of infection in high-risk phase while spreading infection to low-risk phase.

The mechanisms by which risk behavior change increases the fraction of transmissions from PHI are different from the mechanism by which long-term sexual partnerships decreases that fraction. Risk behavior change alters the distribution of infected individuals across the risk phases in a way that individuals with PHI are more prevalent (in terms of the fraction) in high-risk phase, where infection level is higher. On the other hand, long-lasting partnerships influence the fraction of transmissions from different stages of HIV infection by altering the fraction of susceptible partners. When partnerships last for a few months to a few years, infected individuals with PHI are more likely to have partnered to already infected individuals,

compared with individuals with later stages of infection. Thus, more sex acts are “wasted” during PHI than during post-PHI and so the fraction of transmissions from PHI decreases.

Risk behavior change over time affects the average number of secondary infections at equilibrium. Index cases who become infected in high-risk phase or infected by individuals with PHI produce more than one secondary cases on average whereas those who become infected in low-risk phase or infected by infected with later-stage infections produce fewer than one case on average. This means that a control program can be more effective when it reduces transmissions occurring in high-risk or from PHI even if the same number of transmissions are eliminated.

## CHAPTER VI

### Conclusions and Future Study

#### 6.1 Summary

We have examined HIV transmissions by stage in models with various real-world details including long-term sexual partnerships, different types of sex acts, and risk behavior change. In Chapter 2, we have addressed the effects of the duration and the concurrency of partnerships on the transmission of HIV by stage in a homogeneous population using an IBM. In Chapter 3, we have examined similar issues to those in Chapter 2 using a DCM. This DCM approximates a stochastic counterpart in Chapter 2 using pair approximation technique. We have derived simple analytical results and also used numerical integration. In Chapter 4, we have extended the model used in Chapter 3 by including two types of sex acts—insertive and receptive. We have examined the effects on HIV transmissions by stage of the difference in transmission rates between these two sex acts. In Chapter 5, we addressed the effects of risk behavior change on transmissions of HIV by stage by breaking the population down into two risk phases—low and high. In the following sections, we summarize our findings.



### 6.1.1 $\mathcal{R}_0$ and endemic prevalence

Several real-world details we examined generates monotonic effects on the  $\mathcal{R}_0$  and/or endemic prevalence of HIV infection. Endemic prevalence and  $\mathcal{R}_0$  monotonically increase with 1) decreasing partnership duration at a given average number of partners, 2) increasing partnership concurrency, 3) decreasing difference in transmission rates between insertive and receptive sex acts. Endemic prevalence was also bigger when individuals fluctuate between low- and high-risk phases.

Transmissions through long-term sexual partnerships generate a local network structure where infected individuals have fewer susceptible partners and more infected partners than the population average. In terms of the correlation measure, this is to say the correlation between susceptible and infected individuals is below one. This local network structure causes infectious sex acts to be “wasted” between already infected individuals. Therefore,  $\mathcal{R}_0$  and endemic prevalence decrease with increasing partnership duration.

Increasing partnership concurrency by increasing average number of partners given a fixed total sex budget slows transmission per partnership while producing on average the same number of total transmissions. This slows depletion of susceptible partners surrounding infected individuals. Thus,  $\mathcal{R}_0$  and endemic prevalence increases with increasing partnership concurrency.

If there are insertive and receptive sex acts,  $\mathcal{R}_0$  is proportional to the product of insertive and receptive transmission rates. It is also proportional to the product of the correlation between susceptible males and infected females, and the correlation between susceptible females and infected males. Given the sum of two transmission rates remains constant, the product of transmission rates and the product of correlations are maximal when two transmission rates are the same. Thus,  $\mathcal{R}_0$  and the

endemic prevalence increase as the difference in transmission rates between insertive and receptive sex acts decreases.

If individuals fluctuate between low- and high-risk phases, susceptible individuals are replenished from low- to high-risk phase while infected individuals are disseminated from high- to low-risk phase. This increases endemic prevalence in the overall population compared with when there is no risk behavior change.

### **6.1.2 The fraction of transmissions from PHI**

The fraction of transmissions from PHI 1) has a U-shaped relationship with increasing partnership duration, 2) is modified by partnership concurrency in a complex manner, 3) increases with decreasing difference in transmission rates between insertive and receptive sex acts, and 4) is larger when there is risk behavior change between low- and high-risk phases.

The change in the fraction of transmissions from PHI by partnership duration can be summarized as follows:

1. short partnerships (e.g., shorter than 30 days): the fraction of transmissions from PHI is almost the same as we expect from the transmission potential of PHI.
2. intermediate partnerships (e.g., a few months to a few years): the fraction of transmissions from PHI is smaller than the fraction of transmission potential from PHI.
3. long partnerships (e.g., longer than a decade): the fraction of transmissions from PHI becomes larger than the fraction of transmission potential from PHI. The fraction of transmissions from PHI is maximal in fixed partnerships.

We have explained these patterns by separately examining the dynamics of trans-

missions in partnerships that began with discordant infection status and in those that began with both members susceptible. The latter partnerships are unimportant when the average duration of partnership is short. They, however, become important as partnership is lengthened and PHI transmissions are more common in these partnerships. The fraction of transmissions from PHI decrease in both types of partnerships as partnership duration increases. As partnership duration continues to increase, however, the fraction of partnerships that began with both members susceptible increases and the fraction of transmissions from PHI in these partnerships is so high that the total population fraction of transmissions from PHI increases again.

We have also explained these patterns of fraction of transmissions from PHI with using correlation between susceptible and infected individuals. The correlation between susceptible and infected individuals is different by stage of HIV infection. Susceptible partners surrounding infected individuals with PHI are infected faster than those surrounding infecteds with later infections (i.e., asymptomatic and late stages) because of higher transmission rate during PHI than later infections. Thus, the correlation with susceptible individuals is lower during PHI than later infections and the higher depletion of susceptible partners surrounding infecteds with PHI reduces the fraction of transmissions from PHI with increasing partnership duration. As partnership duration continues to increase, however, individuals progress from PHI to later infections while maintaining their partners who might have been infected during PHI. Combined with additional transmissions during later infections, this causes the correlation with susceptibles to be lower during later infections. This then causes the fraction of transmissions from PHI to rise again. Therefore, the fraction of transmissions from PHI has a U-shaped relationship with partnership duration.

Partnership concurrency changes the effects of partnership duration on the fraction of transmissions from PHI. If partnership duration is short (e.g.,  $\leq 1000$  days), the fraction of transmissions from PHI increases with increasing partnership concurrency. By contrast, in longer partnerships, the fraction of transmissions from PHI is higher in lower partnership concurrency.

If a fraction of the population engages in insertive sex acts and the other fraction in receptive sex acts, the fraction of transmissions from PHI in the overall population decreases as the difference in transmission rates between two types of sex acts increases.

Risk behavior change over time (e.g., on the scale of a few months to a few years in high-risk phase and nine times longer in low-risk phase) increases the fraction of transmissions from PHI. If individuals fluctuate between two risk phases, the fraction of infected individuals with PHI increases in high-risk phase whereas later-stage individuals become more prevalent in low-risk phase. This increases the fraction of transmissions from PHI in the high-risk phase and in the overall population.

### 6.1.3 DCMs with pair approximation

In this thesis, we use two types of models— IBM and DCM—and it would be worthwhile to summarize our findings by model type. In this section, we summarize our findings from DCM with pair approximation.

One benefit of using a DCM with pair approximation is that we can get an analytical formulation for  $\mathcal{R}_0$ . Unlike common  $\mathcal{R}_0$  formulations, our formulation includes parameters representing sexual partnerships. In particular,  $\mathcal{R}_0$  formulation in Chapter 3 has two parameters representing sexual partnerships: rates of new partnership formation and dissolution of existing partnerships. And the ratio of partnership formation rate to dissolution rate indicates the average number of partners per person.

$\mathcal{R}_0$  decreases monotonically with increasing partnership duration (i.e., decreasing partnership dissolution rate) at a given average number of partners and with decreasing average number of partners at a given partnership duration (i.e., decreasing partnership formation rate at a given partnership dissolution rate). The fractional contribution to  $\mathcal{R}_0$  of PHI has a U-shaped relationship with increasing partnership duration at a given average number of partners and increases with average number of partners at a given partnership duration.

In Chapter 4, we have extended the model by including two types of sex acts—insertive and receptive. In addition to what is presented in Chapter 3,  $\mathcal{R}_0$  and the fractional contribution to  $\mathcal{R}_0$  of PHI monotonically decreases as the difference in transmission rates between insertive and receptive sex acts increases.

#### 6.1.4 IBMs

In Chapters 2 and 5, we have used IBMs. IBMs give the modeler more flexibility to include real-world details. For example, in DCMs used in Chapters 3 and 4, we assumed partnerships form and dissolve randomly. Using an IBM in Chapter 2, however, we let people with partners have lower rates of new partnership formation than single people. This assumption allowed the distribution of partnerships across the population to vary from monogamy to random Poisson partnerships depending on the difference in partnership formation rates between people with and without partners. Thus, this allowed us to examine the effects of the partnership distribution across the population on the endemic prevalence and the fraction of transmissions from PHI. Endemic prevalence and the fraction of transmissions from PHI increase as partnership distribution varies from serial monogamy to random Poisson partnerships.

In Chapter 5, we extended the model from Chapter 2 by assuming that individuals

can be at either low- or high-risk phase and they fluctuate between the risk phases over time. We showed that endemic prevalence and the fraction of transmissions from HPI are bigger when there is a risk fluctuation between the risk phases compared with when there are two risk phases, but there is no fluctuation between them.

## 6.2 Suggestions for future research

### 6.2.1 Robustness assessment

To get more robust inferences, we can extend our models in a few aspects.

#### Partnership patterns

In this thesis, sexual partnerships across the population have been represented as monogamy, Poisson random graph, or a distribution that lies between monogamy and a Poisson random graph. It appears, however, that the number of partners per person, e.g., the number of partners per person for a given year, has a distribution that is not well captured by monogamy or Poisson random distribution. For example, Liljeros *et al.* [64] showed the number of partners per person in a Swedish population over the course of a year follows a Power-law distribution. Although it is debatable whether the Power-law distribution best describes the observed distribution [66, 67], adopting more realistic distribution of sexual partnerships or, rather, more realistic mechanisms for formation and dissolution of sexual partnerships will be important to make our inferences more robust.

#### Population structure

A population is typically a collection of heterogeneous individuals. To take population heterogeneity into account, we included two types of sex acts in Chapter 4 and two risk phases in Chapter 5. A real-world population is, however, undoubtedly more complex. For example, in some models of HIV transmission, a population was

divided to 6 or more subgroups [44, 45]. It is worthwhile to extend our model to include multiple population subgroups and to test whether our inferences are robust to incorporating multiple subgroups.

### 6.3 Implications of our research

Finally in the following sections we discuss how our simple models and inferences from those models can be useful for answering real-world public health questions or understanding HIV transmissions in more complex situations.

#### 6.3.1 Evaluating the effectiveness of HIV control programs

Our models can be useful for analyzing the effectiveness of a HIV control program. In a recent study [80], the authors evaluated the effectiveness of various HIV intervention programs in Andra Pradesh state of India. First, to estimate the baseline probability of infection without control programs, they used the Weinstein formula:

$$Pr = 1 - \left[ P [1 - R(1 - FE)]^N + (1 - P) \right]^M, \quad (6.1)$$

where  $Pr$  is the probability of HIV infection in uninfected,  $P$  is the average HIV prevalence among sex partners of the group for which probability is being estimated,  $R$  is the risk of HIV acquisition per act of unprotected sex,  $F$  is the fraction of sex acts in which condom is used,  $E$  is the effectiveness of condoms,  $N$  is the average number of sex acts per partner and  $M$  is the average number of sex partners.

Then, the probability of new infection in the target population was calculated by multiplying  $Pr$  with the fraction of susceptible in the target population. Finally, expected number of new infections were calculated by multiplying the population size.

Various control programs such as *MSM programmes* and *Migrant labourer programs* change parameter values such as  $N$  or  $M$  or  $F$  and thus will change the

number of new infections. Instead of using the Weinstein formula, we could use our pair-approximation models to estimate the number of expected cases. The average number of sex acts per partner  $N$  and the average number of sex partners  $M$  provide the basic information to specify our model structure. It would be worthwhile to see how the effectiveness of control programs changes by taking underlying network structure into account. For example, according to the study [80], in the target population of *STI clinics*, the number of sex partners is four per year and the number of sex acts with each partner is twenty five. On the other hand, in the target population of *MSM programmes*, the number of sex partners is twenty per year and the number of sex acts with each partner is five. This implies that the partnerships are long-lasting in the target population of STI clinics whereas partnerships in the target population of MSM programmes change more rapidly. The effects of underlying networks on the effectiveness of control programs will be quite different in these two cases.

Similarly, we can use our models to analyze the effectiveness of other kinds of control strategies such as a partially effective vaccine as in the studies [81, 82, 83, 84, 85], in which case we can set the effects of a vaccine to vary by stage of infection.

### **6.3.2 Understanding HIV transmissions in a complex situation**

Inferences from our simple model are useful for understanding HIV transmissions in a more complex situation. For example, a recent simulation study of a Zambia epidemic [86] shows that the majority of the infected women were infected by their husbands during PHI whereas the majority of those husbands were infected by commercial sex workers during later stages. Infection of their wives by infected husbands is similar to infection transmission in fixed networks in the sense that their partners (i.e., the wives) remain the same over the course of HIV infection of husbands. In



this case, transmission during later stages can occur only if transmissions did not occur during PHI. Thus, the fraction of transmissions from PHI is large. Infection of those husbands by commercial sex workers is different. Men and commercial sex workers do not have steady relationships - their relationships do not last to cover the course of HIV infection. This situation is similar to infection transmissions in short-term or intermediate partnerships. Thus, the fraction of transmissions during PHI is relatively smaller than in the case of fixed networks.

## APPENDIX

## APPENDIX

This thesis was produced using L<sup>A</sup>T<sub>E</sub>X. The numerical analysis of DCMs was done using MATLAB<sup>®</sup> 7.0.1.24704 and Berkeley Madonna<sup>®</sup> 8.0.1. In particular, algebraic calculations were done using MATLAB with Symbolic Math Toolbox<sup>™</sup> 5.

IBMs were written in Java and were run on a cluster of Linux (Redhat) workstations at the Center for the Study of Complex Systems at the University of Michigan, Ann Arbor.

Graphics were produced using SigmaPlot 10.0, Python 2.5 with Matplotlib v0.99.0, and MATLAB.

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