

## ABSTRACT

Title of Dissertation: THE NON-LINEAR TRANSMISSION DYNAMICS  
OF HIV/AIDS

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How infectious a person is when infected with HIV depends upon what stage of the disease the person is in. We use three stages which we call *primary*, *asymptomatic* and *symptomatic*. It is important to have a systematic method for computing all three infectivities so that the measurements are comparable. Using robust modeling we provide high-resolution estimates of semen infectivity by HIV disease stage. We find that the infectivity of the symptomatic stage is far higher, hence more potent, than the values that prior studies have used when modeling HIV transmission dynamics. The stage infectivity rates for semen are 0.024, 0.002, 0.299 for primary, asymptomatic and symptomatic (late-stage) respectively. Implications of our infectivity estimates and modeling for understanding heterosexual epidemics such as the Sub-Saharan African one are explored.

Most models are compartment models that are based on the number of new infections per unit time. We create a new risk-based model that focuses on a

susceptible person's risk of becoming infected if he has a single contact with an infected individual.

THE NON-LINEAR TRANSMISSION DYNAMICS  
OF HIV/AIDS

by

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Dissertation submitted to the Faculty of the Graduate School of the  
University of Maryland, College Park in partial fulfillment  
of the requirements for the degree of  
Doctor of Philosophy  
2004

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## ACKNOWLEDGEMENTS

Thanks to Dr. James A. Yorke and Dr. Frederick Suppe for their knowledge and guidance. To members of the Chaos group at the University of Maryland for providing an environment of sharing and support. To my family, especially my mom and sister, for their years of encouragement. A special thanks to Steven Killi for not only being my computer support, but for his love, understanding, dedication and strength.

Support provided by the National Science Foundation under Grant No. 0104087 and Texas Tech University.

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## Chapter 1

### Determining Infectiousness of HIV

#### 1.1 Introduction

Our goal is to determine how the infectiousness of semen of HIV infected men varies by stage of disease. The actual infectiousness will vary from person to person so we will compute an average. It will also depend on the type of sexual act, higher for some types than for others. We find that susceptible gay men involved in unprotected receptive anal intercourse (RAI) are 12.5 times as likely to become infected when the partner is an infected symptomatic man than when the partner is in the primary stage; that is, symptomatic men are 12.5 times as infectious as primary men. Furthermore, asymptomatic-stage men are 149.5 times less infectious than symptomatic men. We expect this general pattern of infectivity to hold for all sex acts of infected men.

We focus on measuring the infectivity of gay men. By the “infectivity” of a person, we mean the fraction of his susceptible “contacts” that he infects. For HIV we interpret a “contact” to be the activity in which most infected gay men became infected [1, 2]. Infectivity varies as the disease progresses in the individual, and of course one cannot conduct experiments to determine infectivity.



In this paper we analyze the San Francisco City Clinic Cohort data, and figure out how many contacts there are at each point in time between susceptibles and infecteds, and what stages of infection those men are in. This is not a straightforward calculation. We take into account the great variability between the contact rates of the men.

*SFFCC Data:* The only high-resolution data set documenting the onset of HIV in a population is the San Francisco City Clinics Cohort (SFCCC) study, which is based on blood samples from an earlier Hepatitis B Vaccine Clinical trial that took place during the period in which HIV exploded through the San Francisco gay population [3, 4, 5] (Table 1.1). That study, involving about 10% of the San Francisco gay population, involved 6875 men and took both blood samples and behavioral data. After HIV was identified, stored blood samples were thawed and tested for the presence of HIV antibodies. This enabled one to document the growth of HIV through the population (Figure 1.1) and relate that growth to behavioral data. We stress that with respect to HIV incidence, that data set is a biological one not dependent on medical diagnosis or infection self-report [4].

*Variable Infectivity:* It is widely understood that epidemiological modeling of HIV transmission must utilize at least three stages (primary infection, asymptomatic, and symptomatic including AIDS) with different infectivities for each stage (Figure 1.2). First comes a period of primary infection (lasting part of a year). Our *primary infectious stage* is defined as the time soon after initial infection when infectiousness first rises and then drops. Seroconversion, the development of antibodies, typically occurs well before the end of our primary stage. One then enters into an *asymptomatic period* (averaging 7-8 years without

Year	% Population susceptible at year end.	% Population infected during year.	% Population symptomatic at year end.	Est.% Population symptomatic at mid-year.
1978	95.5			
1979	85.9	9.6	0	
1980	73.8	12.1	0.1	0.05
1981	68.6	5.2	0.55	0.32
1982	51.5	17.1	1.72	1.13
1983	39.3	12.2	3.56	2.64
1984	32.6	8.5	5.85	4.7

Table 1.1: SFCCC HIV Onset Data. Susceptible and infected fractions (Columns 2 and 3) for each year (Column 1) are from the published sources (3,4). The percent of the population symptomatic at year-end (Column 4) is derived from the Figure 1.1 optimized solution of the stage/sub-stage model of HIV transmission. These show reasonable agreement with 1987 estimates [6] doubled to correct for the 1993 redefinition of AIDS [7]. The estimated % of the population symptomatic at mid-year (Column 5) is the average of this and the previous year's year-end symptomatic fractions.

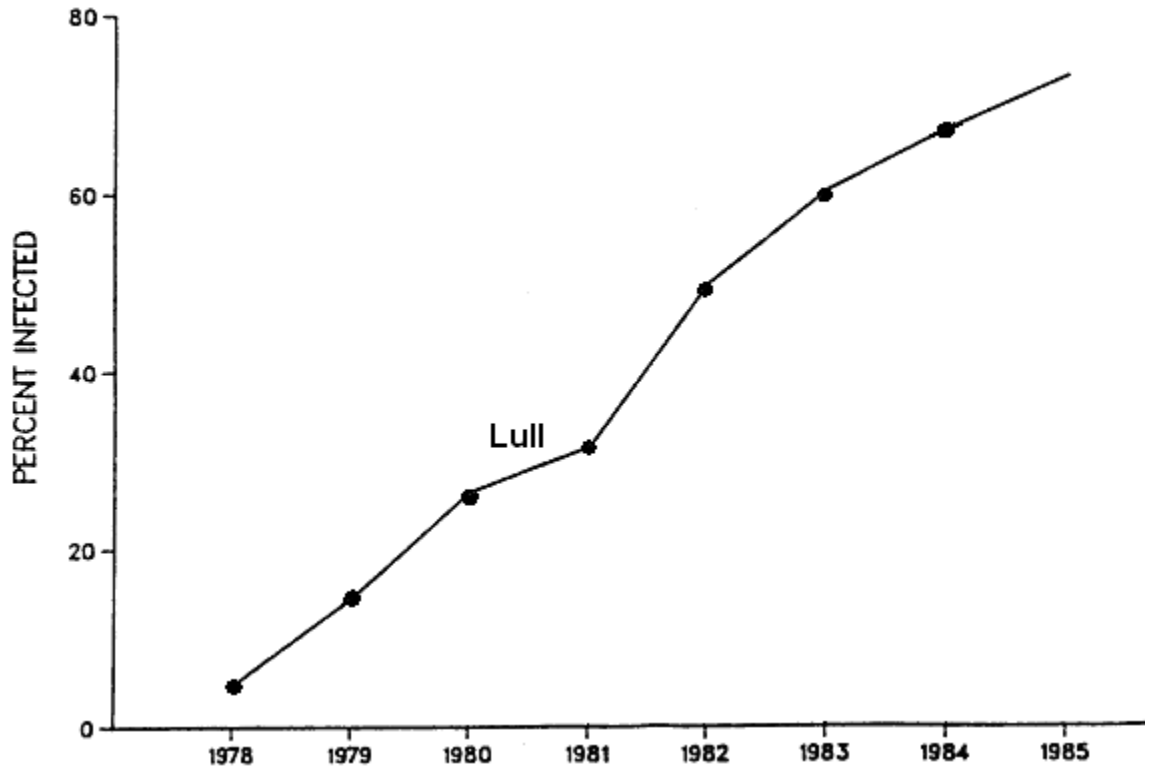


Figure 1.1: Growth of HIV infection through the SFCCC [4] Note the 1980-1981 “lull” wherein the epidemic slows down before explosively restarting the next year. This phenomenon in the data has not been addressed in the epidemiological literature modeling the SFCCC epidemic data. (It may be a statistical artifact.) Our modeling shows that this lull can be reproduced only in variable infectivity models where late-stage (symptomatic) transmission dominates the epidemic once about 30% of highly promiscuous populations are infected.

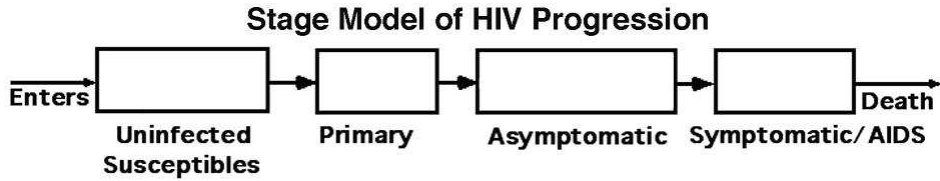


Figure 1.2: HIV stages [9] and infectiousness. A susceptible becomes newly infected and progresses from a primary infection stage through an asymptomatic stage into a symptomatic stage followed by death. Infectiousness varies greatly from stage to stage.

treatment) in which infectiousness is very low, followed by a *symptomatic stage* (averaging three years until death without treatment) where infectiousness rises again. The symptomatic stage begins while individuals are relatively healthy and active though it also includes the more severe AIDS phase. These average times are based on SFCCC data [8].

Viral levels also vary greatly between these three stages. During the period of primary infection viral levels are typically high. The viral levels become low as one enters into the asymptomatic period, followed by a symptomatic/AIDS stage where the viral loads are extremely high [10, 11, 12] (Figure 1.3).

If one assumes, plausibly, that HIV infectivity correlates with semen viral levels [13, 14, 15, 16] then one would expect that HIV transmission is more infectious during the primary infection and symptomatic stages than during the asymptomatic stage and is even more infectious during the symptomatic stage.

Note: Our model does not use information about viral loads, but obtains results showing that infectivity follows a pattern similar to the viral loads shown in Figure 1.3.

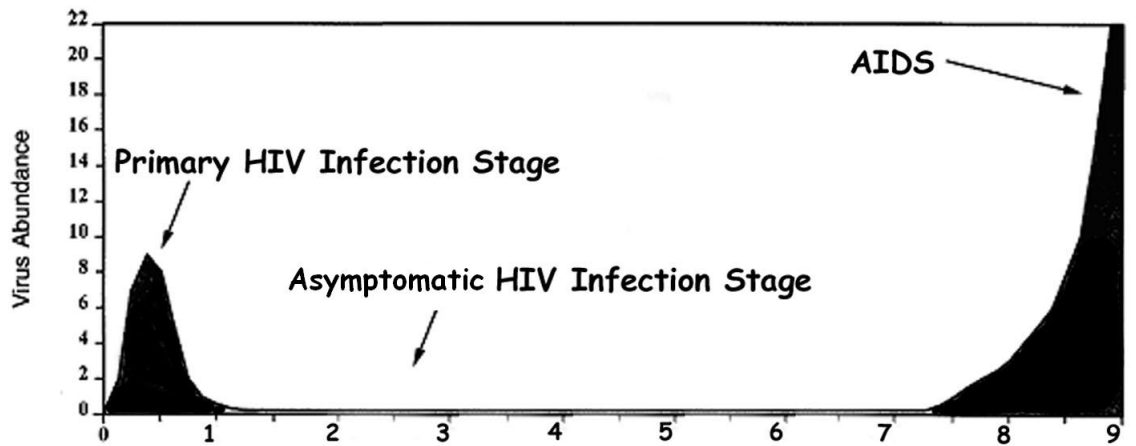


Figure 1.3: Variable viral loads over the course of a typical untreated individual’s HIV infection (source: Reworked from Anderson [13]).

That primary stage plays a significant role in the original gay HIV epidemic is widely understood due to epidemiological modeling by Jacquez, Koopman, Hethcote and Van Ark, Ahlgren, Longini, and others [6, 8, 17, 18]. None of these prior studies attributes a significant role to late-stage symptomatic transmission in shaping the epidemic. A frequently referenced paper, Jacquez et. al. 1994 [18], says “a review of the data on infectivity per contact for transmission of the HIV suggests that the infectivity may be on the order of 0.1 to 0.3 per anal intercourse in the period of the initial infection,  $10^{-4}$  to  $10^{-3}$  in the long asymptomatic period, and  $10^{-3}$  to  $10^{-2}$  in the period leading to AIDS.” They obtained the primary and asymptomatic-stage infectivities by looking at the initial growth of the epidemic and determined what infectivities would be necessary to create such an exponential growth. In contrast to those results that are carefully obtained via detailed models, they say without giving any details that the symptomatic-stage infectivity was estimated using previous partner studies [19, 20, 21] and in

most cases heterosexual partner studies. It is unclear how those stage estimates were obtained, since those studies do not differentiate infectivity per stage, but had an “average” infectivity for the course of the disease. We remark that in [[22], (see Figure 1 page 56)], one can see that there is a negative correlation between the number of contacts a couple has and the probability that the disease will be transmitted. For couples with more contacts it was reported less likely for the susceptible partner to become infected. Ahlgren [8] reported they were unable to obtain reliable estimates of symptomatic-stage infectivity using data on reported incidence of AIDS infections. In the early epidemic those data are very unreliable due to underreporting, mis-diagnosis, and changing definitions of AIDS in estimating symptomatic-stage infectivities. Our approach relies neither upon those prior partner-study estimates nor problematic reported AIDS incidence data.

*Activity Levels:* The SFCCC reports annual numbers of partners for six different activity levels [6, 8](Table 1.2). The most active half have more than 10 times as many contacts as the lower half. By 1982 almost half the population was infected, presumably primarily the most active half. The most active 10% (the “core”) are responsible for nearly half of all sexual contacts [23].

Published survey data gives the distribution of the number of partners for six activity levels, but does not give receptive anal intercourse (RAI) group averages. However, the data indicate that for the overall population 57% of the contacts involved RAI by at least one of the two partners [8, 24], so we estimate RAI activity for each group at 57% of total activity. Note: If the RAI is for only one partner then we are over-estimating the number of contacts by a factor of 2, resulting in a 50% underestimation of stage infectivities, but not affecting the

Group I	Size $F_j$	Contacts/year $C_j$ Group	Fraction of All contacts
1 ("Core")	10%	231	0.48
2	15%	81	0.25
3	25%	33	0.17
4	25%	15	0.078
5	15%	3	0.009
6	10%	0	0.000
Total Pop	100%	48	

Table 1.2: Group RAI Contact Behavior. Group contact data (Columns 1-3) are from reference [6]. Group fraction of all contacts is the total number of annual RAI contacts for the group (Column 2 – Column 3) divided by the population average of 48.

ratios of stage infectivities. Thus we divide the population into 6 groups based on this estimated average RAI activity (= contacts). Average number of RAI partners per year is 48 [8, 25]. These estimates are Column 3 of Table 1.2.

Most prior (homosexual) studies [8, 12, 26] either did not differentiate activity groups or else had only two groups, a highly active “core” group consisting of 5-10% of the population and a less active non-core. Models with only one or two activity groups give results which differ significantly from the six-group model.

Available evidence suggests that unprotected sexual activity did not decrease significantly until 1985 [27]. For this reason we model the epidemic through 1984 with no behavioral change. We also assume that each individual’s sexual activity level is the same for all three stages of the infection. We later discuss the effect

of modifying these two modeling assumptions.

*Mixing Patterns:* We model interactions among six activity groups, obtained from published SFCCC survey data, as if all sexual contacts were casual and promiscuous—such as was typical in gay bathhouses where contacts are fairly indiscriminate and casual. Our **bathhouse assumption** is that gay contacts resemble bathhouse patterns. More specifically, published SFCCC data gives average contact rates for six different activity levels. We assume these specify the average frequency with which persons go to the bathhouse, but once inside the mixing pattern is random. Thus the bathhouse assumption addresses both the frequency of contacts and the mixing pattern when contacts occur. Since the core has nearly half of all contacts, nearly half the men in the bathhouse at any given time are in the highly active, promiscuous core. Figure 1.4 shows that there are fewer susceptibles in the bathhouse than in the general population—an essential fact in understanding the epidemic.

A key to understanding the dynamics of an HIV epidemic is estimating from population totals how different activity-level groups of uninfected people become infected (Figure 1.5). Our modeling reveals that very early in the epidemic the core group [28] rapidly becomes infected. The infection spreads through other groups more slowly. Core members are responsible for 48.5% of all sexual contacts (Table 1.2). Once most of the core is infected, new infections predominantly are of group 2 men until they too are mostly infected. Then most new infections will be of group 3 men, and so on (Figure 1.5).

*Infectivity Estimates:* The only transmission vector for homosexual transmission of HIV to be shown epidemiologically significant is via receptive anal intercourse (RAI) [29]. It is standard to interpret HIV infectivities for gay men



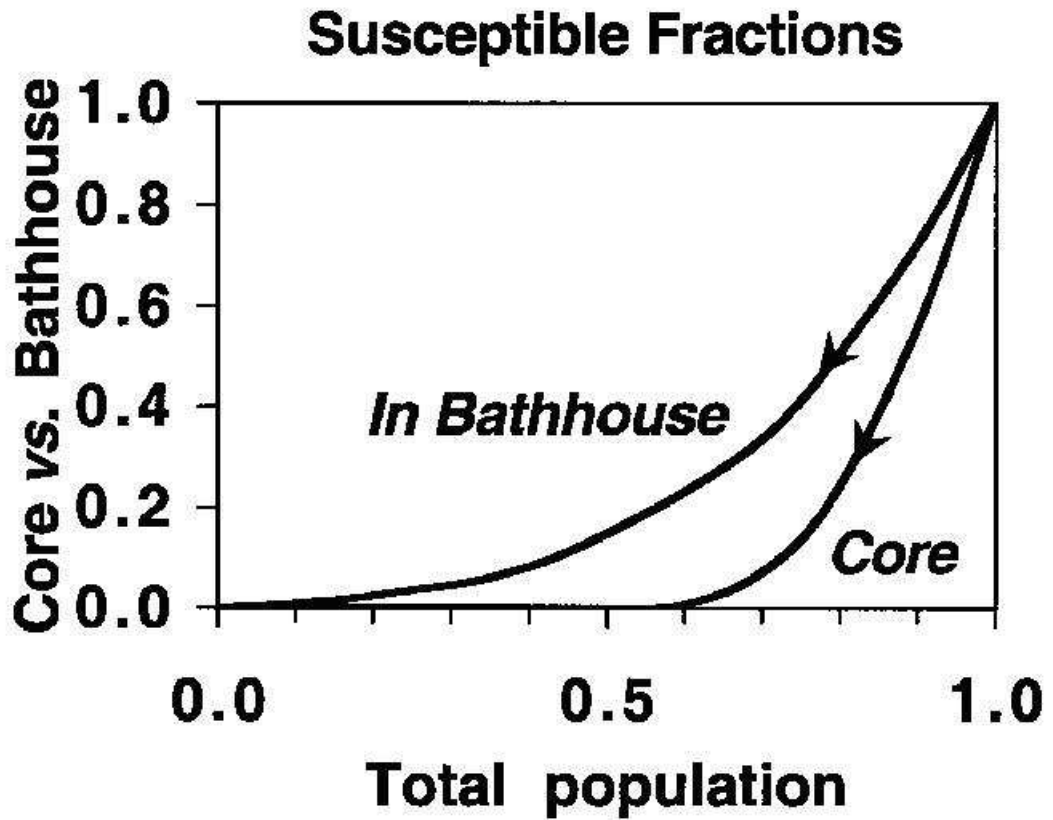


Figure 1.4: Susceptibles in more active groups are soon depleted. An essential finding of the distribution problem solution is that there are fewer susceptibles in the bathhouse than the general population and even fewer members of the most active groups present in the bathhouse will be susceptible. For example, if 60% of the population is susceptible (as was the case in mid-1982), we can conclude that 23% of the men in the bathhouse are susceptible and virtually none of the Core members present will be susceptible.

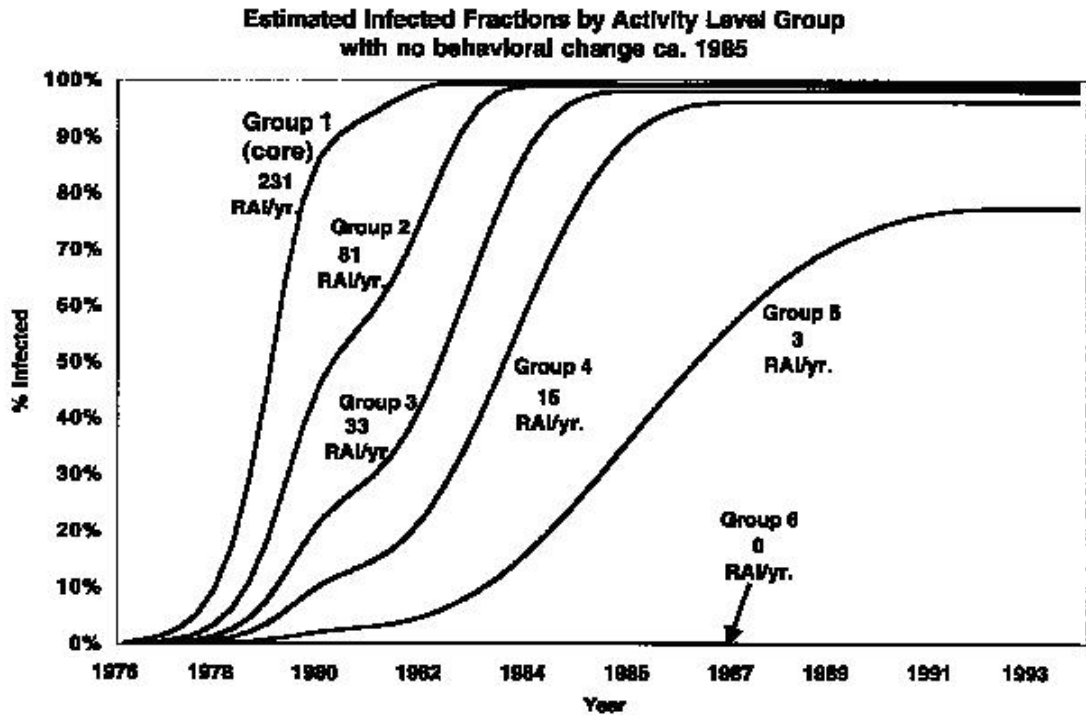


Figure 1.5: Fraction of Infecteds in the Bathhouse by Activity Group: The susceptible fraction of the entire population over time has been partitioned into susceptible fractions for each of six different activity groups over time. Our “bathhouse” assumption is that men vary greatly in how often they make themselves available for sex, that is “choose partners in the bathhouse,” but once inside the bathhouse the choice of partner is rather indiscriminate and every susceptible man’s per-contact chances of becoming infected are equal. In the bathhouse susceptibles are similarly determined. More active persons usually get infected sooner than less active persons. The susceptibles for more active groups drop faster than in less active groups. The graph shows (along with Figure 1.4), for example, that when total population susceptibles dropped to 46% (in mid-1983), only 12% of men in the bathhouse were susceptible and virtually none of the core were. Method: Model Equation, see Appendix A

as RAI infectivities. Early studies that did not consider difference in contact rates and did not estimate different infectivities for the three stages came up with a 1% infectivity for RAI. It is not unreasonable to construe these estimates as the average infectivity of an individual over the course of his HIV infection (i.e., as the average of the stage infectivities weighted by stage durations).

*Stage Transitions:* It is well established that, in the first approximation, a typical untreated HIV infection progresses through the stages defined by successively high, low, and then very high viral levels in the blood<sup>1</sup>. For the SFCCC the average durations of each stage are well documented and confirmed by modeling [8]. The problem is that those averages are based on some people who pass through stages to AIDS faster and others who pass through slower or perhaps never become symptomatic or develop AIDS. This is only an issue for the relatively long asymptomatic and symptomatic AIDS stages. A good model needs to have some sort of diffusion pattern producing different rates of passage through those stages. Since there are no data regarding such “diffusion”, the simplest way to model this is to allow sub-stages where the number of sub-stages determines the diffusion gradient. Then one can choose how many sub-stages to use depending on accuracy of best fit to HIV incidence with different numbers of sub-stages. Our basic model does this, and does come up with three diffusion sub-stages for the asymptomatic period and one stage for symptomatic/AIDS (Figure 1.6).

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<sup>1</sup>Individuals undergoing anti-retroviral treatment (ART) tend to progress to AIDS at a much slower rate than untreated individual[30].

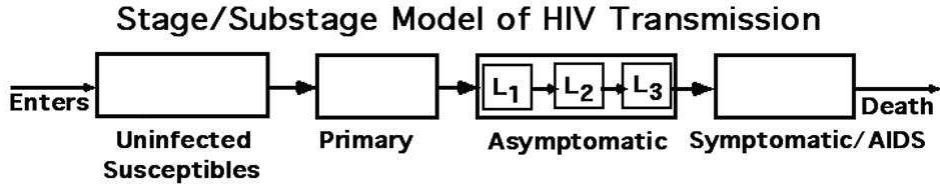


Figure 1.6: Schematic representation of model used for optimized fits to SFCCC epidemic. Three sub-stages have been added to the asymptomatic stage in Figure 1.2. These sub-stages adjust the standard deviation of the mean time spent in that relatively long stage. Method: Choice of three sub-stages was determined by optimization studies.

## 1.2 The Basic Model

Our *basic modeling principle* is that the constants in our model should be based on epidemiological data. We avoid *a priori* assumptions not supported directly or indirectly by data.

*The Stage Model:* For primary infection the sub-stages amount to the assumption that the average time after infection that one infects is a quarter of a year. The peak of the viral load occurs at one quarter of a year [13].

We assume that susceptibles are in three-month cohorts moving through susceptible and HIV-infection stages as determined by the following variables and equations where  $i, j =$  Activity groups 1 (core), 2, ..., 6;  $k =$  Primary, Asymptomatic, Symptomatic (AIDS); and  $t = 1, 2, 3, \dots$ . We assume primary infection lasts two time periods but that all primary-stage transmission occurs at the end of the first time period, i.e., 1/4 year. We assume that new susceptibles enter the population at the same rate at which there are AIDS deaths. We now define the variables used in our model.

Susceptible fraction of group  $i$  at time  $t$ :  $S_i^t$

Primary first fraction of group  $i$  at time  $t$ :  $P_{1,i}^t$

Primary second fraction of group  $i$  at time  $t$ :  $P_{2,i}^t$

Asymptomatic first fraction of group  $i$  at time  $t$ :  $L_{1,i}^t$

Asymptomatic second fraction of group  $i$  at time  $t$ :  $L_{2,i}^t$

Asymptomatic third fraction of group  $i$  at time  $t$ :  $L_{3,i}^t$

Symptomatic fraction of group  $i$  at time  $t$ :  $A_i^t$

Death fraction of group  $i$  at time  $t$ :  $D_i^t$

Partnering Rate of group  $i$  with group  $j$ :  $r_{ij}$

Infectivity of persons in group  $j$  at stage  $k$ :  $a_{jk}$

Fraction of group  $j$  that is in stage  $k$  at time  $t$ :  $f_{j,k}^t$

Duration of Asymptomatic sub-stage (7/3):  $d$

Time step (in terms of fraction of a year):  $\Delta t$

New group  $i$  Primary fraction # 1:

$$P_{1,i}^{t+1} = S_i^t \left[ \sum_j \sum_k r_{ij} a_k f_{j,k}^t \right] \quad (1.1)$$

New group  $i$  Primary fraction #2:

$$P_{2,i}^{t+1} = P_{1,i}^t \quad (1.2)$$

New group  $i$  Latent Asymptomatic fraction #1:

$$L_{1,i}^{t+1} = L_{1,i}^t + P_{2,i}^t - \frac{L_{1,i}^t}{d} \Delta t \quad (1.3)$$

New group  $i$  Latent Asymptomatic fraction #2:

$$L_{2,i}^{t+1} = L_{2,i}^t + \frac{L_{1,i}^t}{d} \Delta t - \frac{L_{2,i}^t}{d} \Delta t \quad (1.4)$$

New group  $i$  Latent Asymptomatic fraction #3:

$$L_{3,i}^{t+1} = L_{3,i}^t + \frac{L_{2,i}^t}{d} \Delta t - \frac{L_{3,i}^t}{d} \Delta t \quad (1.5)$$

New group  $i$  AIDS fraction:

$$A_i^{t+1} = A_i^t + \frac{L_{3,i}^t}{d} \Delta t - \frac{A_i^t}{3} \Delta t \quad (1.6)$$

New group  $i$  Death fraction:

$$D_i^{t+1} = \frac{A_i^t}{3} \Delta t \quad (1.7)$$

New group  $i$  Susceptible fraction:

$$S_i^{t+1} = S_i^t - P_{1,i}^{t+1} + D_i^{t+1} \quad (1.8)$$

From this model we can derive:

Population cumulative Infected fraction:

$$I_i^t = \sum_{i=1}^6 [2 * P_{1,i}^t + L_{1,i}^t + L_{2,i}^t + L_{3,i}^t + A_i^t] \quad (1.9)$$

Population seroconversion rate:

$$C^t = \sum_{i=1}^6 P_{1,i}^t \quad (1.10)$$

*Model parameters:* Most model parameter values are specified using SFCCC data: Average time from seroconversion (development of antibodies) to death reportedly was 10.3 years [8]. In our model, the average primary infectious period lasts for 1/2 year although seroconversion typically occurs at around 3 months. When we tried shorter primary-stage periods such as 1/3 year we were unable to fit the data as well. The epidemic behaves as if semen remains infectious for a bit longer than the usual primary-stage period. Thus the average duration of an HIV infection is 10.5 years. The remaining parameters are determined by best-fit approximation to the 1978-1984 SFCCC HIV infection growth data. Thus every parameter value in the stage model is either a firm SFCCC datum or is highly

constrained by the SFCCC data. No unconstrained parameter assumptions are employed.

*Interpreting the Stage Model:* The San Francisco population is divided into 6 activity groups and each group is divided into 3 stages of infection (primary, asymptomatic and symptomatic). To run our model, the user specifies the fraction of the men in each stage at an initial time  $t_0$ , and the three infectivities for the three stages of infection.

Given the fraction of each activity group that is in each stage at time  $t$ , the rules built into the model dictate what the corresponding fractions will be at time  $t + \Delta t$ , where  $\Delta t$  is a specified fraction of a year. We typically took  $\Delta t$  to be 1/4 or 1/3 year for the time step, and we report results here for 1/4 year though the results for 1/3 are similar. The model takes these fractions and takes another time step, applying the same procedure to get the corresponding fractions for time  $t + 2\Delta t$ . The model takes a certain specified number of steps that is long enough for it to create a record of an outbreak similar to San Francisco's. For a detailed description of the model's bookkeeping see Appendix B.

*Initializing the model:* We do not know when the epidemic actually began in San Francisco. Nor do we know the initial state. Nor does it matter. No matter how we initialize the outbreak (whether the initial man or men are highly active or less active or in primary stage or symptomatic stage) we must choose an initial time so that the epidemic reaches the prevalence (i.e., the fraction infected) of 4.5% in 1978, the time of the first prevalence report. By that time and there after, the distribution of infected people is essentially independent of how we started the epidemic. As long as the initial infected fraction is small, the long-term shape of the plot of prevalence is not affected. The first prevalence report from SFCCC

was 4.5% in 1978.

### 1.3 Determining the “best-fit” Infectivities

*Obtaining “best-fit” infectivities for the three stages:* Estimates of average infectiousness for each of the three stages are obtained using the Figure 1.6 model and our model equations. For any choice of the three infectivities the model can be run, and an epidemic is produced. In particular the cumulative fraction infected is reported for each of the seven years from 1978 to 1984. For each of the seven years we compute the square of the difference between this model epidemic and the actual SFCCC epidemic. Let RMS denote the square root of the average of those seven numbers.

$$RMSError = \left( \frac{1}{7} \sum_{1978-1984} [S_{model}(t) - S_{actual}(t)]^2 \right)^{1/2} \quad (1.11)$$

We use a minimization technique to select the choice of infectivities for which the RMS is minimized [4, 13, 31]. We take the gradient of the  $(RMSError)^2$  and use Newton’s method to find a 0 of the vector field. The minimum is obtained for stage infectivity rates approximately 0.024, 0.002, and 0.299 respectively with an RMS of 0.016 (Figure 1.7). We call these infectivity estimates the “best-fit infectivities”. The model solution displayed in Figure 1.7 reproduces the “cumulative SFCCC epidemic” using these best-fit infectivities.

*The epidemic for the best-fit infectivities:* Figure 1.8 shows that before 1980 about 98% of the infections were caused by primary-stage men who only have been infected for a few months<sup>2</sup>. By 1981 this fast transmission wave ends when

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<sup>2</sup>We can understand much of the early dynamics without finding a solution to the model.



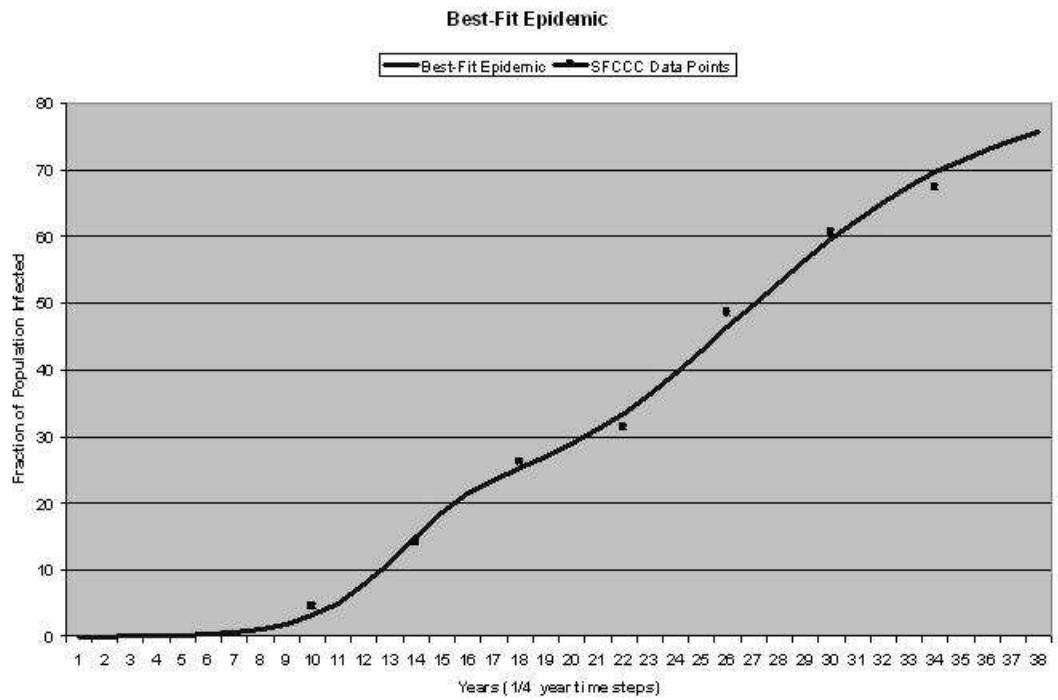


Figure 1.7: Best-Fit Epidemic: The best-fit epidemic is produced by running our model with the best-fit infectivities (0.024, 0.002, 0.299). This produces an RMS error of 0.016.

most of the highly active men are infected and are in the asymptomatic stage. After 1981, these men begin entering the symptomatic stage and cause most of the new cases. This second wave is a slow transmission wave where the infectors are mostly symptomatic men who have been infected for years and are now highly infectious. The 1980-81 lull [3], shown in Figure 1.1, if not an artifact, is consistent with low infectivity for asymptomatic men. Symptomatic men are more than 12 times as infectious as primary-stage men for perhaps four times as long, making the gay slow-transmission wave extremely lethal. Figures 1.8 and 1.9 reveal the epidemic's structure: It is the combined effects of the displayed fast-transmission wave before 1980 followed by the displayed slow-transmission wave.

## 1.4 Implications of Infectivity Estimates

*The infectiousness of semen:* Our goal has been to determine how HIV transmission-infectivity varies as the infection progresses within a typical individual not receiving medical treatment, using available data. We conclude symptomatic-stage individuals are about 12.5 (i.e.,  $0.299/0.024$ ) times more infectious (per contact) than primary-stage men and about 149.5 (i.e.,  $0.299/0.002$ ) times more infec-

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Of course any active man could have got infected and then infected others, but it is instructive to focus on the core and only the infections they caused when in the primary stage. Those men had 231 partners per year or about 115 in the primary stage (1/2 of a year). 48% of those contacts (or 55 contacts) are with core men. The primary-stage infectivity is 2.4% resulting in 1.3 infections. Some of these infections are in the first quarter year and some in the second and the average time to infection is 1/4 year. Hence, each quarter of a year the number of infected men grows by a factor of 1.3. The result of 4 such steps (1 year's worth) is a growth of a factor of 3. We see then that the core primary-stage men in San Francisco were able to drive the first (fast) wave of the epidemic.

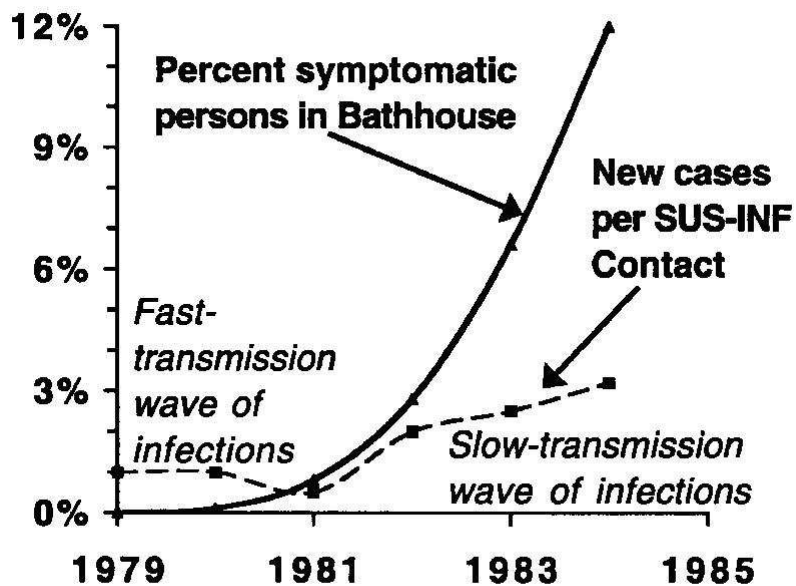


Figure 1.8: The solid curve shows increase of symptomatic men in the bathhouse where transmission takes place. Symptomatics do not become a significant presence in the bathhouse until 1981 when 31% of the population had been infected in the fast wave. Average “infectiousness,” the dashed line, is the percent of susceptibles infected by a contact with an infected man in the bathhouse (labeled as “new cases per Susceptible-Infected contact”). Early in the epidemic, when most transmissions are from primary-stage men, infectiousness is 1%. Later in the epidemic, during the slow transmission wave, infectiousness triples as men in symptomatic stage begin transmitting HIV. Since they are a small fraction of the infected men in the bathhouse, their average infectiousness must be at least 17%-28%. Methods: Based on model equations.

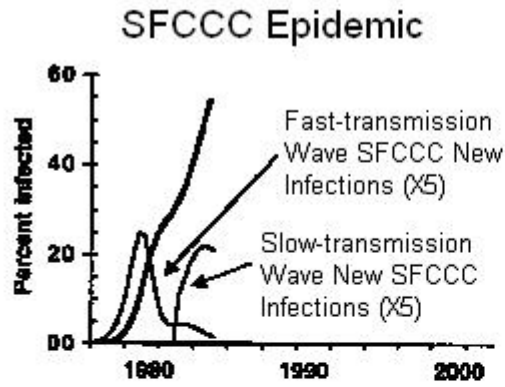


Figure 1.9: Two-wave Gay Epidemic: Primary stage per-contact infectivity is 1.9%, asymptomatic 0.2%, and symptomatic 30%. The model has solutions that closely approximate the SFCCC incidence data only when the infectivities are close to these infectivity levels. Primary-stage men drive the fast-transmission wave; symptomatic men dominate the slow-transmission wave. Methods: Based on model equation.

tious than asymptomatic-stage men. We interpret the infectivities more loosely as measures of the infectiousness of semen in the three stages. Doing so enables us to apply our infectivity estimates to heterosexual transmission. Specifically, we would expect rather similar ratios for the stage probabilities of men infecting women contacts. The actual stage infectivities for vaginal intercourse might be higher or lower, depending on the type of contact, but the effective stage ratios would be similar. We have no way to measure the corresponding infectiousness of women. In modeling heterosexual populations, we assume that these effective contact ratios are similar for men and women and apply equally across stages <sup>3</sup>.

*Effective contact rates for the stages:* Now we take into account the duration of the stage. If all the partners of a man were susceptible, then for each contact per year the number of men we would expect him to infect is the product of infectivity and duration. It is 0.012 men ( $= 0.024 * 1/2$ ) for primary-stage men, 0.014 ( $= 0.002 * 7$ ) for asymptomatic, and 0.897 ( $= 0.299 * 3$ ) for symptomatic-stage men. We call these the “effective contact rates for the stages”. These numbers measure the relative danger of the three stages to all their susceptible partners. The effective contact rate for the symptomatic stage is 75 times that of the primary stage ( $= 0.897/0.012$ ) and about 64 ( $= 0.897/0.014$ ) times that of the asymptomatic stage. Hence if the great majority of a man’s partners are susceptible, then during the symptomatic stage, he is likely to infect 75 times as many partners as when he is in the primary stage and 64 times as many as in the latent stage. That does not mean the primary period is unimportant, since in San

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<sup>3</sup>Studies of heterosexual populations show that untreated infected individuals viral loads follow a pattern of moderate, then low, then high as a person progresses through the disease [32, 33, 34, 35]. This corresponds to the pattern of our infectivity estimates.

Francisco primary contacts were the main method of transmission, up through 1980. It instead suggests how truly dangerous the symptomatic stage is.

If an average infected man contacts  $N$  susceptibles per year, over the course of his infection he will contact  $10.5N$ , since the average duration of infection is 10.5 years. Furthermore, he will infect  $0.923N$  men over the course of his infection, where 0.923 is the sum of the effective contact rates from above ( $0.012 + 0.014 + 0.897$ ). We calculate the fraction of the people infected by each stage as follows:

$$P_1 = 0.012/0.923 = 0.013 \quad (1.12)$$

$$P_2 = 0.014/0.923 = 0.015 \quad (1.13)$$

$$P_3 = 0.897/0.923 = 0.972 \quad (1.14)$$

So over 97% of infections a man causes are transmitted when he is in stage 3 (note that  $P_1 + P_2 + P_3 = 1.0$ ). Recall this is assuming that almost all partners are susceptibles, but it also holds when the fraction of partners that are susceptible remains constant, as when the epidemic is in equilibrium in the population. The often repeated assertion that the primary stage plays the most significant role in driving an HIV epidemic holds only when the epidemic is growing very rapidly such as it did in San Francisco before 1981.

*The mean transmission time:* When a person is infected, we refer to the “transmission time” as the length of time the infector was infected at that point in time. For example if someone is infected by a person in his/her primary stage, the transmission time would be about 0.25 years on the average while if the infector was in stage 2 or 3, the transmission time would be about 4.0 or 9.0 years respectively on the average, the times from initial infections to the middles of the stages.

When an epidemic is at equilibrium the mean transmission time is computed by weighting these three times by the fraction of people infected in that stage.

$$(P_1 * .25 + P_2 * 4.0 + P_3 * 9.0) = 8.81years \quad (1.15)$$

If the epidemic is not at equilibrium but is growing, then there are two possible patterns. In the first pattern there will be relatively more people who were recently infected than infected longer ago. In a growing epidemic, when a susceptible finally meets an infected person, that person is more likely to be in the primary stage, as happened in San Francisco prior to 1981 (Figure 1.9). A more precise calculation would take into account the exponential rate at which the epidemic is growing. In the second pattern the majority of people come from those in the third stage. The second pattern characterized San Francisco after 1981 (1981-1985) and Sub-Saharan Africa throughout their course.

*Sub-Saharan Africa:* Estimating mean transmission times allow us to extend our findings to Sub-Saharan Africa and other heterosexual populations. It is not known when the first case of HIV occurred in Africa, but it is believed to have been around 1950 or perhaps earlier [36]. From 1950 to 1990, less than 1% of the population was infected as the number of cases went from 1 to about 1,000,000 producing a slow transmission wave [37, 38, 39]. We estimate the mean transmission time about  $T = 7.44$  years based on our values of infectivities when an epidemic grows by a factor of 1,000,000 in 40 years. We now can estimate how difficult it would be to stop the epidemic:  $R_0$  is defined to be the *average* number of secondary cases caused by an *average* infected individual at the beginning of the epidemic when almost all are susceptible. Stopping the epidemic quickly requires interventions that result in driving  $R_0$  well below 1. Let the number of

generations  $G = 40/T$  5.4. If the epidemic grows by a factor  $R_0$  for each of  $G$  generations the compound growth is  $R_0^G$  which should equal about 1,000,000. Our estimate that  $T = 7.44$  yields  $R_0 = 13$ . This calculation depends on the infectivities and duration of the stages and not on other aspects of our SFCCC model.

If an epidemiologist assumes the epidemic started, say in 1930, the argument changes, yielding  $R_0 = 4.3$ , but still remains well above 1. In either case, major sociological changes are necessary to drive  $R_0$  below 1. If the epidemiologist was not aware of the importance of the symptomatic stage and assumed that the epidemic was driven by the primary stage, the mean transmission time would be short. For the sake of argument we take it to be 1 year. Then there are 40 generations and  $R_0$  would be 1.4. This incorrect assumption would lead to an underestimation of the severity of the epidemic. Only relatively small changes would be necessary to bring  $R_0$  below 1, stopping the growth of the epidemic.

We remark for San Francisco a reduction of the effective contact rate by a factor of 101 would have been necessary to prevent the epidemic from growing early on in the epidemic (Figure 1.10). In other words,  $R_0$  was 101 for SFCCC.

## 1.5 Methodological Discussion of Modeling Assumptions

We want to know whether our results are artifacts of our modeling assumptions. In this section we discuss our preferred use of six activity groups in our modeling rather than the two or one activity groups used other researchers; the tacit assumption of persisting levels of sexual activity; random mixing on the bathhouse



### Equilibrium Levels

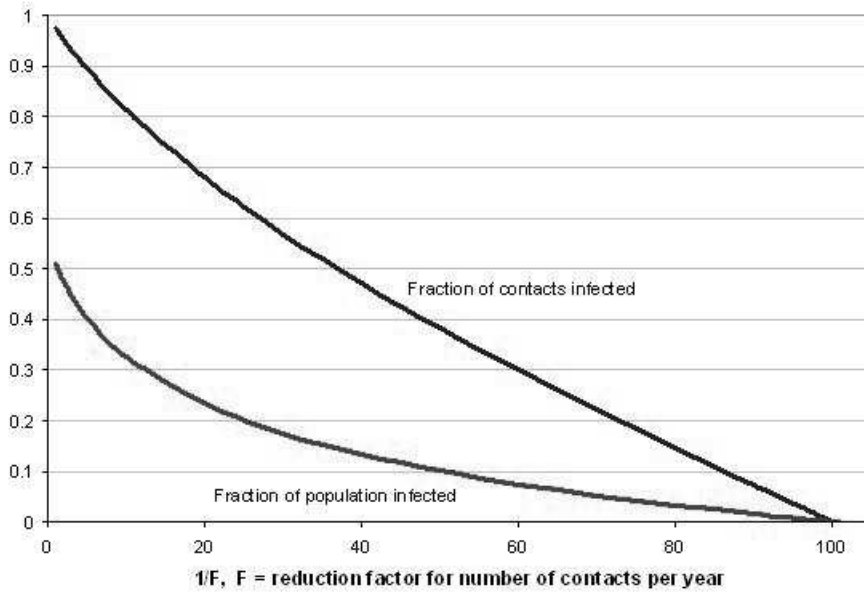


Figure 1.10: Equilibrium Levels. At any average annual contact rate, over time, an epidemic will stabilize at some fraction of the population infected. What this equilibrium level is depends on the average annual number of contacts. The graph displays equilibrium levels ranging from the SFCCC ( $F = 1$ ), to contact rates 1/100th of the SFCCC ( $F = 100$ ). Whenever  $F < 101$  the equilibrium results in some portion of the population infected, thus  $R_0 = 101$ . The SFCCC peak is 70.2% where as the equilibrium level is 50%.

assumption; and the use of deterministic rather than stochastic models.

*Six-Group Model Assumption:* Earlier variable-infectivity models [8, 6, 17, 18, 26, 40, 41] used at most two activity levels instead of our six. Core vs. non-core models capture the importance of primary-stage infectivity in initiating the gay epidemic but underestimate and thereby miss the critical role of symptomatic-stage infectivity in sustaining and intensifying the gay epidemic after 1980 and in initiating and sustaining slow transmission epidemics, such as Sub-Saharan Africa. We compared our six-group assumption by making new optimization fits to the SFCCC incidence curves using two-group and one-group models.

We use the 6-group model because it maximally utilizes the available contact data. What happens if we use simplifying assumptions that do not take full advantage of these data? The major difficulty of a two-group model is choosing the number of contacts for each of the groups. The infectivities will depend upon the level of activity of the two groups. Even if the first group (the core) is 10% of the population it is unclear how to choose a single average number of contacts for the remaining 90% of the population. Consider a two-group core/non core model with non-core members having 27 contacts per year (two-group model A in Table 1.3/Figure 1.11), the actual numerical average. Note that this average includes group 6 whose members have no contacts. Surely, they should not be included, but group 5 has almost no contacts (3 per year) and they have almost no effect on the epidemic. Probably they should not be included. Group 4 has 15 contacts per year, enough to be significantly important in the epidemic, but it plays much less of a role than groups 2 and 3 with 81 and 33 contacts per year. Our two-group model B instead uses a weighted average to obtain a non core average number of contacts of 53 per year, weighting the groups in proportion

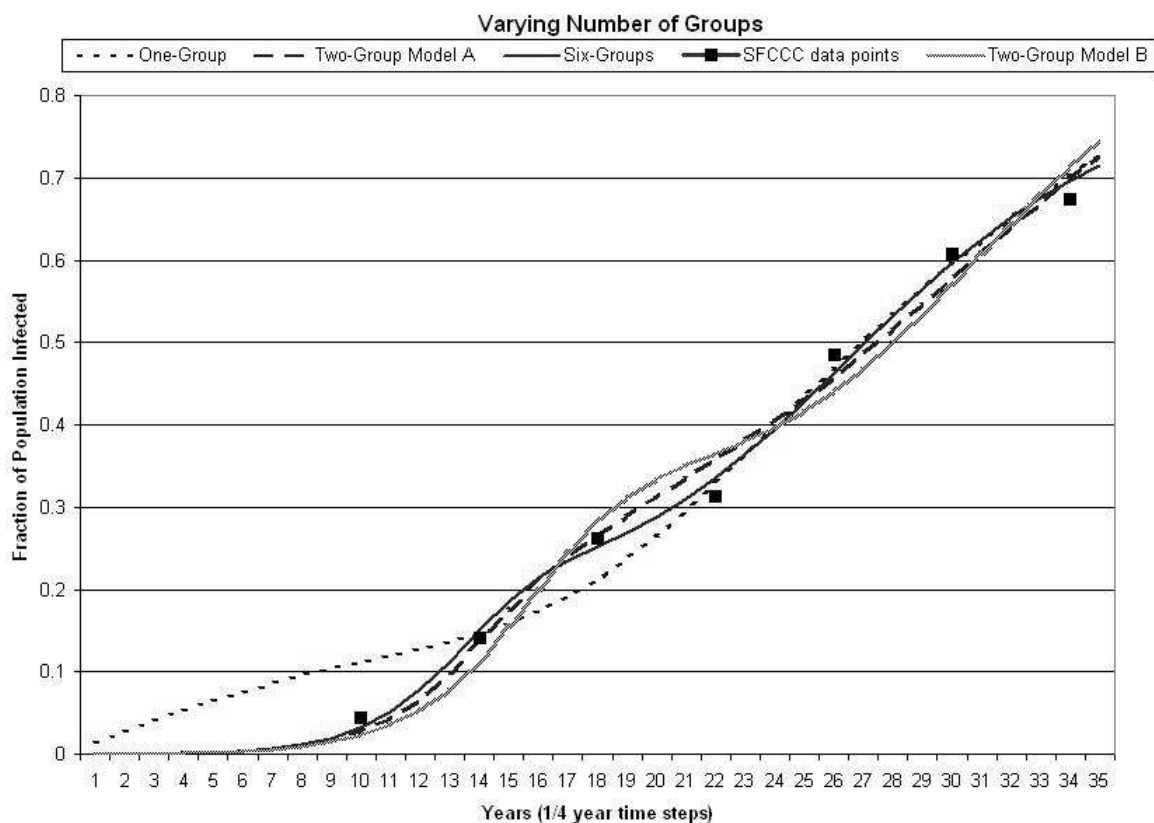


Figure 1.11: Comparison of our 6, 2 and 1-group model. The one-group model cannot account for the initial growth of the epidemic. The six-group model has the smallest RMS-error and gives the best-fit to the SFCCC data points.

to the number of contacts they have. In fact, neither model A nor model B is perfect, which emphasizes the need for six groups, reflecting the SFCCC survey data.

Changing our model to two-group model A yields 0.024, 0.005, 0.091 optimized infectivities for primary, asymptomatic, and symptomatic stages – resulting in an underestimate of symptomatic-stage infectivity by about 2/3. (This is in keeping with results in prior two-group studies.) Two-group model B results in

		Best-Fit Stage Infectivity Estimates			
	Average Number of Contacts Per Year	Primary	Asymp	Symp	RMS Error Of Fit to SFCCC data points (Equation 1.12)
Six-Group Model	See Table 1.2	0.024	0.002	0.299	0.016
Two-Group Model A	231:10% 27: 90%	0.024	0.005	0.091	0.025
Two-Group Model B	231:10% 53: 90%	0.028	0	0.089	0.037
One-Group Model	48	0.042	0	0.088	0.035

Table 1.3: Comparison of our Six-Group, Two-Group and One-Group Models. It follows from the equations for each of these models that if all the contacts per year are changed by a fixed factor, for example doubled, then all the infectivities are reduced by that factor, i.e. cut in half. The one-group model produces epidemics that always severely disagree with the San Francisco data and cannot explain slow epidemics such as the African one. Both the two-group and the one-group models underestimate symptomatic stage and thereby cannot explain slow epidemics such as the African one.

optimized infectivities of (0.028, 0.0, 0.089). Once again, the symptomatic stage is underestimated by about 2/3.

Similarly, if we collapse all six activity groups into a single average activity level, then in the best optimized one-group model the symptomatic stage is underestimated (0.045, 0.000, 0.088). The goodness-of-fit error is 0.03 compared to 0.016 for our six-group optimization fit. Even with high symptomatic-stage infectivities a one-group model is unable to capture the beginning of the San Francisco epidemic prior to 1979 (Figure 1.11). Details about the comparisons between the different group optimized models are given in Table 1.3.

What these comparisons show is that using fewer than six activity groups increasingly makes infectivity estimates be artifacts of the simplifying assumptions such as core/non-core or a single activity group used in prior modeling. The six activity-group models reflect the diversity of the population and reflect the reported data. What they teach us is that late in the disease, when more than half of the population is infected, lower sexual activity groups are being infected but the epidemic is accelerating. The SFCCC data show large numbers of persons become infected, but there are fewer contacts with susceptibles because those still susceptible have few contacts. Most of these infections result from partners in the symptomatic stage. This requires a higher symptomatic-stage infectivity estimate than previous models which failed to reflect the low activity of remaining susceptibles. After 1980 the gay epidemic becomes dominated by symptomatic-stage transmission.

*Constant Sexual Activity Levels Assumption:* The data we use is from the San Francisco epidemic up to 1984. We have assumed that each individual has a sexual activity level that does not change significantly over the period we are

modeling. The Bell-Weinberg study [42], a Kinsey Institute study of the 1969 San Francisco Population, found that the most active 28% of men had 51 or more partners “in the past year”. The study also found that the men who were most active over their lifetimes (again 28%) had 1000 or more partners (see Table 1.4). Such a total requires many years of high activity levels—perhaps one or two decades or longer. Our model is appropriate for such a population. Of course there will be some individuals who change behavior but a large fraction of the most active “core” population will remain highly active when they are in the symptomatic stage. The epidemic went from 4.5% infected to 60% in just 5 years.

One can hypothesize populations with variable activity levels. Some earlier models assume that individuals vary in their activity level over time. For example, Koopman et al. [26] assume this variation is quite rapid. They use two activity levels: a core with 5% of the population and the less active non-core. They assume that individuals remain in the core for an average of one year, saying, “Our models are not intended to reflect the transmission dynamics of any real population” ([26], page 250). The assumption implies there is virtually no correlation between the activity level of a man when he becomes infected and the activity level a few years later when he is in the symptomatic stage. (Under that assumption, the probability of an individual in the core will remain in the core for say 6 years is  $\exp -6$  or  $\sim 1/400$ ). Having people rapidly switch activity levels is quite similar to assuming there is a single activity level.

Some may suggest, quite plausibly, that it is likely people in the symptomatic stage are less active due to effect of HIV. If so, then the symptomatic-stage infectivity would have to be higher than our .299, to account for the large number of observed cases. This can be described by a mathematical relationship. If you

Number of Homosexual Partners Ever	%	Number of Homosexual Partners in Past Year	%
1	0	0	3
2	0	1-2	8
1-2	1	3-5	10
3-4	2	6-10	12
5-9	3	11-19	12
10-14	3	20-50	27
15-24	8	51+	28
25-49	9		
50-99	15		
100-249	17		
250-499	15		
500-999	15		
1000+	28		

Table 1.4: Bell- Weinburg Survey of 572 Homosexual Men in San Francisco in 1969 [42].

cut the number of contacts in half uniformly, for the symptomatic stage and for all activity groups, then the optimal symptomatic-stage infectivity would be doubled in order not to decrease the number of new infections below the observed level.

In order to account for the large number of new infections in the latter stage of the epidemic, where most of the susceptibles were from low activity groups, one must have high symptomatic-stage infectivity. Only the six-group models are able to determine the high level of infectivity in the symptomatic stage.

*Model Assumes no Decrease in Activity as the Epidemic Explodes:* What if activity levels dropped as the epidemic progressed? It is likely that activity levels began to drop as people became aware of some new gay disease around 1984 or 1985 [8]. We have tried alternatives to our model, for example, by cutting the contact rate in half in 1983-1984. We then again determine the infectivities for the three stages that result in the best fit of the data. The main effect is that the symptomatic-stage infectivity must be higher than in our standard model. The infectivities of the first two stages are largely determined by the need to fit the pre-1981 beginning of the epidemic when there are very few symptomatic-stage men. Decreasing the activity while maintaining the number infected results in higher symptomatic infectivity. Our main conclusion in this dissertation is that the symptomatic stage is far more infectious than the earlier stages. Our conclusion remains valid when there is a decrease in sexual activity level as the epidemic progresses. Our symptomatic-stage estimate, although higher than what prior studies report [8, 18, 26], is in fact a lower bound. Indeed, Hethcote and Van Ark's assumption of decrease activity beginning in 1981 requires them to use an AIDS-stage infectivity of 0.75 to model the SFCCC data [6].



*Model Without Age Structure:* The bathhouse assumption supposes casual promiscuous gay sex with random mating. The Bell-Weinberg data (Table 1.4) suggest the bathhouse assumption is appropriate for this population. However, some researchers have hypothesized that random mating is inappropriate on the assumption that people prefer to partner with persons close to their own age. We do not employ such an age-preferred model (in which partners are selected based in part on their ages) because the data do not support one. Koopman et al. [26] considered an age-preferred model with eight 2-year age groups. Their “age-preferred” mixing pattern assumes 80% of partnerships are reserved for one’s own age group and the other 20% are the result of proportionate mixing independent of age. This pattern however is difficult to achieve: for example, assume that people’s ages are uniformly distributed within each age group and that the age of a person’s partners is normally distributed with the mean equal to the person’s age. For a person to have 80% of his partners within his own age group (under the Koopman et al assumption of 2-year age groups) then on average the standard deviation would be about 0.5 years. Under the best of conditions it would be extremely unlikely that people would be able to estimate someone’s age within 0.5 years. In the SFCCC the majority of sexual contacts were between men who were strangers and one-time partners [42, 43, 44, 45]. A disproportionate fraction of the core contacts occurred in bathhouse orgy rooms, which typically were virtually dark. It is extremely difficult to make gross distinctions of age in the dark. Making a half-year distinctions seem impossible. Even if we considered an age-preferred model with age groups of 5 years, the standard deviation would be approximately 1.3, still extremely unrealistic for the San Francisco population.

*Stochastic versus Deterministic Models:* Our model is a deterministic model.

At each time step we determine the fraction of individuals who transition from one stage of infection to the next for each activity level, such as from core susceptible to core primary infection. We also developed a stochastic model where at each time step we first compute the fraction of people who would make each transition according to the rules of our deterministic model and convert this to a number of men by considering the late 70s-early 80s San Francisco gay population to be an estimated 70,000 individuals [31]. Using this fraction as a mean, we select a random number from a Poisson distribution. This random number becomes the number of individuals who make the transition at that time. The epidemic is then simulated repeating this Poisson process for each time step and for every transition (See Appendix C for stochastic model equations). We find the biggest differences between the epidemics of the deterministic model and the stochastic model occur when the fraction of people infected is very small. By the time the fraction infected reaches 4.5% (as was the case in 1978, the SFCCC first data point) both models generate very similar curves.

Since we are using the same three infectivities in both models our confidence in these three infectivities increases: When their results are congruent, there is negligible harm in using a deterministic model even when a stochastic model theoretically might seem more appropriate. Both approaches require high levels of symptomatic-stage infectivity compared to primary-stage infectivity.

We conclude that, compared with the assumptions used by other researchers, ours are more realistic and/or appropriate when applied to the SFCCC population. Our finding that symptomatic-stage infectivities are about thirty-times higher than previous estimates is not an artifact of our assumptions.

## 1.6 Discussion of Modeling Conclusions

*Testing the conclusion symptomatic infectivity is greater than primary infectivity:*

To further test this conclusion we examine the cases where the two infectivities are equal. For comparison we ran our optimization code with the added constraint that the primary-stage infectivity equals the symptomatic-stage infectivity. The “best-fit” infectivities are 0.0, 0.02, 0.0 respectively for the three stages and the RMS error is 0.036. Note the RMS is more than twice the RMS error for “best-fit” infectivities mentioned previously. With this constraint there is no “best-fit” with positive values for the primary and symptomatic-stage infectivities.

*Sensitivity analysis for SFCCC data:* Although the SFCCC HIV incidence data are unusually high resolution and biologically based, they still are subject to measurement and sampling errors. By our estimate, the 4.5% prevalence figure might better be reported as  $4.5 \pm 1.3$  % representing a one standard deviation error. The method for computing prevalence for other years is reported with less detail and we cannot compute standard deviations for those years. Further the behavioral data are self-reported. Studies indicate such self-reported behaviors among gay men are quite reliable [43, 44, 45]. Nevertheless there are errors inherent in such data.

When we vary the fraction of population that is infected for the data points 1978 through 1984 by about 0.02 and then apply the above optimization procedure, we get slightly different infectivities for our three stages. In summary, primary-stage infectivity varies in the range 2.3-2.5%, asymptomatic from 0.0-0.4%, and symptomatic/AIDS from 25.4-34.4%. Figure 1.12 shows us the region of uncertainty.

*Interval of Infectivity Estimates:* Our infectivity results must be valid for

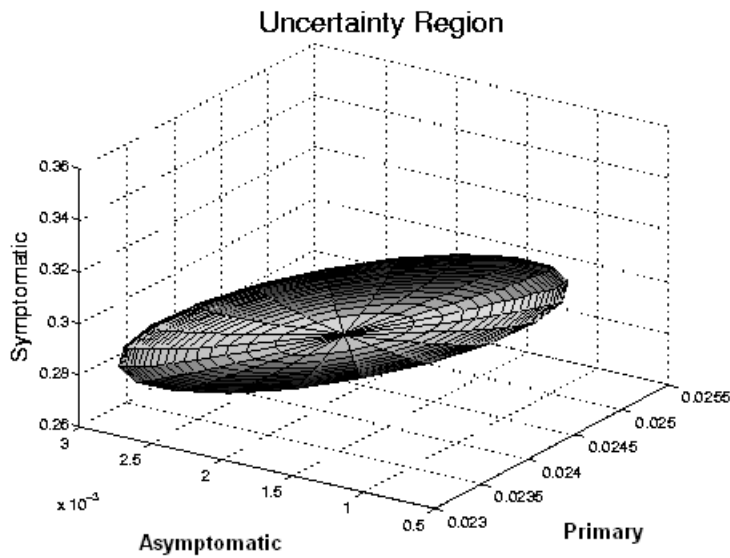


Figure 1.12: Sensitivity Analysis. The three infectivities for our three stages depend on the reported epidemic data for years 1978 through 1984. There is an inherent error in the data, perhaps 1-2%. If these data points are changed by a (root-mean-square) average of 2%, the infectivities lie on the ellipsoid shown. If they are changed by 4% the size of the ellipse will be doubled in each direction. If they are not changed, they lie at the center of the ellipsoid.

variations in model parameters<sup>4</sup>. Earlier we discussed error in the data points and the effect that variations in the data would have on our infectivity results. We also mentioned the differences between stochastic and deterministic models. Infectivities would increase if we considered a behavior change before 1985 due to knowledge of the disease or associated with progression of the disease. We could also take into account the possibility of preferential mixing, in which one chooses partners within their own group. If one does not allow those in lower activity groups to have contacts with those in the core and other more active groups, then in order for the epidemic to rip through the six groups as shown in Figure 1.5, the third-stage infectivity would have to be even higher than our estimates. This conclusion holds when one considers a combination of the bathhouse mixing and preferential mixing.

Allowing all combinations of parameters mentioned above, we end up with intervals of infectivity estimates. The primary stage varies within (0.014-0.024), the asymptomatic (0.000- 0.008)<sup>5</sup>, and the symptomatic (0.126-0.493). We are interested in the ratio of the symptomatic-stage infectivity to the primary-stage infectivity, which varies (8.6-33.7). So we conclude that even under variations of our model parameters the symptomatic stage remains significantly more infectious than the primary stage.

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<sup>4</sup>Our model has a time step of 1/4 of a year, 2 sub-stages for the primary period, 3 sub-stages for the asymptomatic period, and one for the symptomatic period. We also considered time steps of 1/3 and of a year, along with 1-2 sub-stages for primary, 1-6 for asymptomatic and 1-2 for symptomatic.

<sup>5</sup>If in our optimization routine an infectivity value becomes negative, we set it to zero. We do not believe that the asymptomatic period is ever truly zero.

## 1.7 Conclusion:

Earlier models shed little light on slow-transmission epidemics such as the African and the San Francisco epidemic from 1980. They are dominated by symptomatic-stage transmission. In addition, they seriously distort the transmission dynamics after 1980: In two-wave epidemics, such as the San Francisco gay one, there is a period when primary-infection stage transmission is the predominant mode of transmission and alone can sustain the epidemic. Only symptomatic-stage infection can sustain a slow epidemic as in Africa. If there is no such period you get an epidemic such as the South African one. Ultimately both epidemic patterns become dominated by symptomatic-stage transmission.

Underestimating the symptomatic-stage infectivity results in a severe underestimation of  $R_0$ , the severity of the epidemic, and the measures necessary to end the epidemic. Our results provide a firm basis for a needed systematic reassessment of prevailing wisdom and strategies concerning the control, containment, and management of the HIV pandemic. Our results imply that screening of at risk populations can identify most infected individuals before they enter their most infectious stage. Removal of symptomatic-stage transmission would reduce  $R_0$  below 1 for many extant at risk populations (though it would not for the SFCCC population).

## Chapter 2

### A Risk Based Model for HIV

#### 2.1 Introduction

Previous models of HIV [8, 6, 17, 18] are compartment based. The compartments represent stages of HIV infection. A person is expected to pass through the stages sequentially as the virus becomes more dominant within the person's body. Those models assume that the time it takes an infected person to pass through a stage is a random variable that is exponentially distributed [6, 46] and that the infectiousness of an individual varies by stage of infection and each stage has its own level of infectiousness. One can derive from such models an "infectiousness distribution" that tells how infectious the average person is time  $\tau$  after initial infection.

The models we present here omit the stages and assumes the infectiousness distribution of an infected man is specified independently of the model. Our approach to creating the models in this chapter focuses on a susceptible person's risk of becoming infected if he has a single contact with an infected individual. The dynamics of traditional models instead are based on number of new infections per unit time. This difference allows us to build a scalar model representing

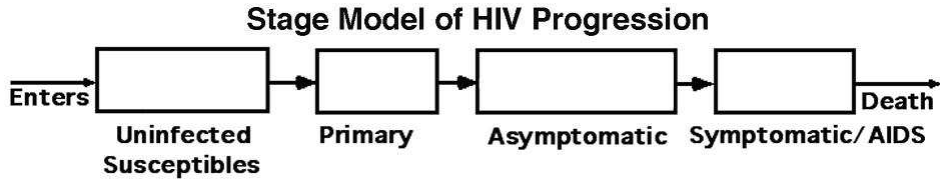


Figure 2.1: HIV stages [9] and infectiousness. A susceptible becomes newly infected and progresses from a primary infection stage through an asymptomatic stage into a symptomatic stage followed by death. Infectiousness varies greatly from stage to stage.

populations with many different sub-groups. Our equation is an integral equation rather than a differential equation. That allows greater freedom in choosing the distribution of infectiousness. To introduce the ideas of our models we begin by creating a model for a homogeneous population. Then we develop our full model in which there is an arbitrary number of groups that have varying levels of sexual activity.

## 2.2 Infectiousness Distribution

The infectiousness of a person is the probability that a contact with a susceptible will result in that person becoming infected. A susceptible can only become infected through such a contact. Previous models, including ours from Chapter one, are compartment models with individuals changing their infectiousness as they change stage of disease. Our model has 3 stages, primary, asymptomatic and symptomatic (Figure 2.1).

We have an infectiousness associated with each stage of infection, 0.024, 0.002



and 0.299 respectively. We call these infectivities our “best-fit” infectivities <sup>1</sup> see Figure 2.2. The motivation behind our new model is to be able to put any curve describing infectivity into our model.

We define infectiousness as a piecewise continuous function  $I : [0, \infty] \rightarrow [0, 1]$  which is the expected infectiousness after a person is infected at time  $\tau$ . As an example, if we assume the infectiousness,  $I_0$ , is constant in each of three stages and the progression from each stage to the next is as described in Chapter 1, then as an average person progresses through the disease their infectiousness varies continuously with respect to time:

$$I_0(\tau) = \sum_{k=1}^3 P_k(\tau) * P_k.infec \quad (2.1)$$

Where  $P_k(\tau)$  is the probability a person infected for time  $\tau$  is in stage  $k$  and  $P_k.infec$  is the infectivity per contact for the  $k^{th}$  stage. For our three-stage model the stages are primary, asymptomatic and symptomatic with the infectivities equal to our best-fit infectivities mentioned above.

We obtain the infectiousness distribution in Figure 2.3 by running our model with the three best-fit infectivities. We allow for one individual to be infected and follow his expected infectiousness as defined by equation 2.1. Note that in the beginning of the epidemic the individual is in the primary stage with probability 1 and thus has an infectiousness of 0.024. The infectiousness drops as

---

<sup>1</sup>The infectivities are obtained from a difference equation model, described in Chapter 1, that finds the three infectivities that best-fit the SFCCC (San Francisco City Clinic Cohort) epidemic. The SFCCC epidemic is based on data collected from gay men that participated in a hepatitis B vaccination trial study from 1978 through 1984. Blood samples and survey data were collected from nearly 7,000 men. The blood samples were frozen and through analysis of these blood samples the number of HIV cases in the gay population in San Francisco were obtained.

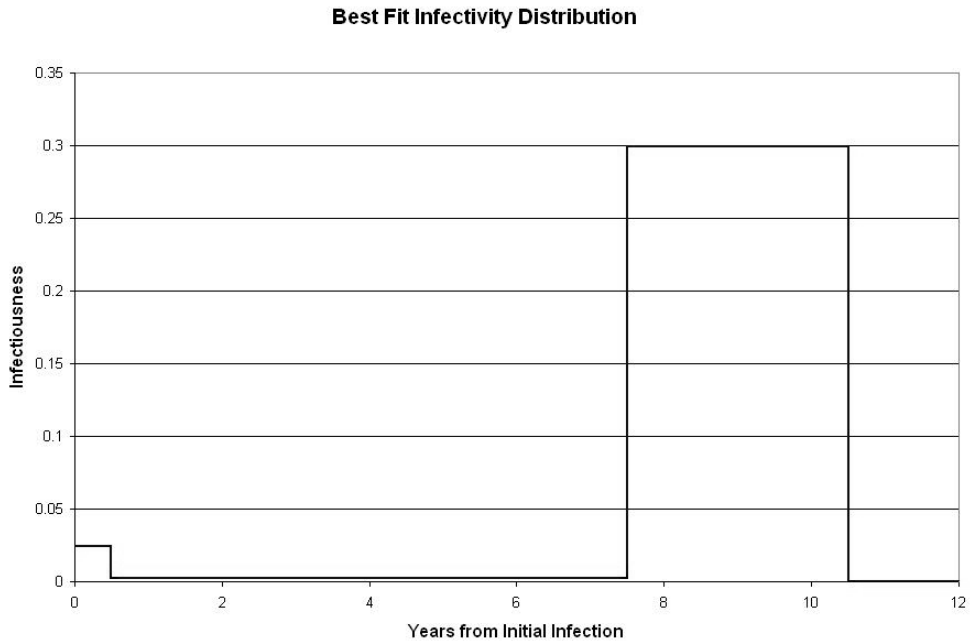


Figure 2.2: Best-fit Infectivity Distribution: Our model described in Chapter 1 solves for the three infectivities that best-fit the SFCCC epidemic. Those infectivities are 0.024, 0.002, 0.299 for the primary, asymptomatic and symptomatic stages respectively. An average individual is in the primary stage for 0.5 years, the asymptomatic stage 7 years and the symptomatic stage for 3 years. This figure shows the average infectiousness of a fictitious person who passes through each stage at precisely the expected time

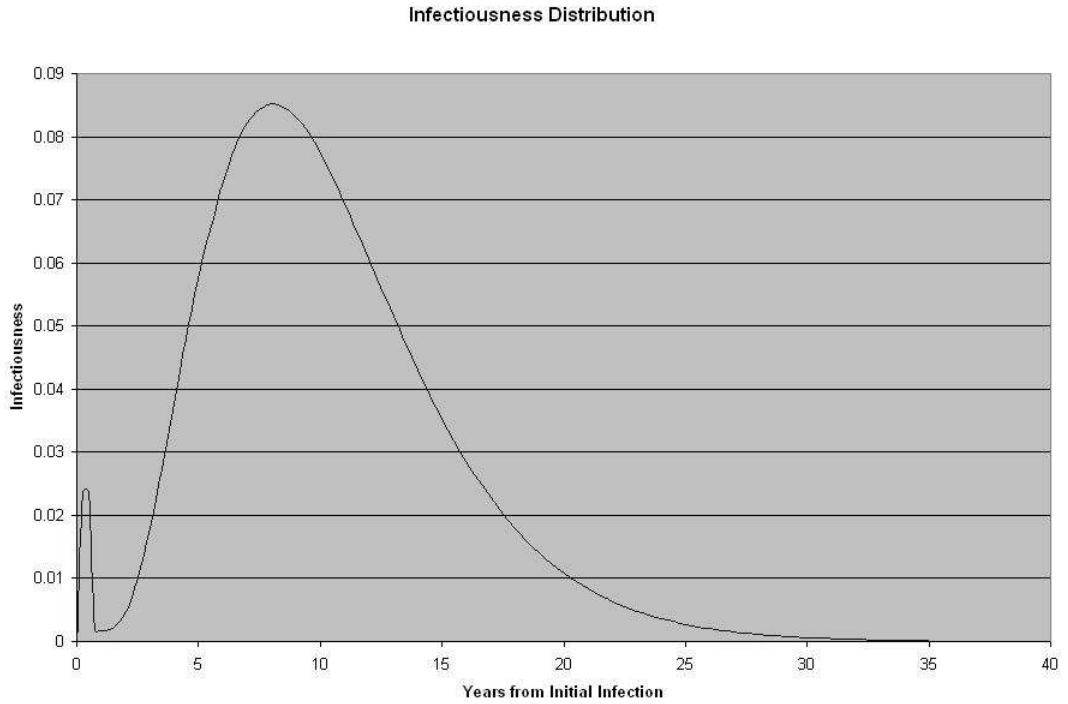


Figure 2.3: Continuous distribution of infectiousness averaged over the population,  $I_0(\tau)$  (Equation (2.1)).

the individual moves into the asymptomatic period, then peaks as the probability they have transitioned into the symptomatic stage increases. The infectiousness begins to decrease as the probability of death increases.

## 2.3 Risk Model and Assumptions

Assumptions

1. After time  $t_0$ , no one enters or leaves the population.

Our goal is to model an HIV outbreak over a fairly short period of time beginning at time  $t_0$ . In fact a very small fraction will die, but, we treat

these as people whose infectiousness is zero. This approach has negligible impact on the transmission dynamics as long as the fraction that is dead is small. This assumption has the effect of lowering the contact rate slightly as people die.

2. Each individual has a contact rate that is independent of  $t$ .

In section 2.4 we will assume all individuals have the same contact rate and in section 2.5 we assume the rates vary from person to person.

3. **Mixing Assumption** The probability of 2 people having a contact is independent of disease status (infected or susceptible) or stage.
4. Infectiousness is independent of the person's contact rate.
5. All susceptibles are equally susceptible.

There is a **risk function**,  $R(t)$ , the probability that any susceptible who has a contact at time  $t$  will become infected. We define the accumulated risk,  $A(t)$ , by

$$A(t) = \int_{-\infty}^t R(s)ds \quad (2.2)$$

Note:  $dA/dt = R(t)$ . Time  $t = t_0$  denotes the beginning of the outbreak.

## 2.4 One-Group Risk Model

We create a model in this section that focuses on a susceptible person's risk of becoming infected if they have a single contact with an average infected individual. We will assume that we are dealing with a homogeneous population; there is one activity group for the given population.

6. Assume all individuals have the same number of contacts per unit time  $C$ .

7. **External Risk Assumption** We assume that prior to time  $t_0$ , the risk is 0, and at time  $t_0$  a transient infected individual is momentarily present and making contacts. We treat this event by assuming  $R$  is a  $\delta$ -function at  $t_0$  with weight  $a$ , so  $\lim_{\epsilon \rightarrow 0} \int_{-\epsilon+t_0}^{\epsilon+t_0} R(s)ds = a$ .

**Proposition 1** *Assume 1-7. Then  $R$  and  $A$  satisfies the system*

$$R(t) = \begin{cases} a\delta(t - t_0) + \int_{-\infty}^t I(\tau)R(t - \tau)C \exp(-CA(t - \tau))d\tau & \text{for } t > t_0 \\ 0 & \text{for } t < t_0 \end{cases} \quad (2.3)$$

$$A(t) = \int_{-\infty}^t R(s)ds \quad (2.4)$$

Let  $S(t)$  be the fraction of the population susceptible at time  $t$  with  $S(t_0) = 1$ .

Then

$$\frac{d}{dt}S(t) = -CR(t)S(t) \quad (2.5)$$

and

$$S(t) = \exp(-CA(t)) \quad (2.6)$$

A susceptible person having a contact at time  $t$  has a chance of being infected by a person who in turn was infected during the interval  $J = [t - \tau, t - \tau + d\tau]$ . We treat the length of the interval as an infinitesimal. So we need to know how many such people were infected during  $J$ . The fraction of the population susceptible at time  $t - \tau$  is

$$S(t - \tau) = \exp(-CA(t - \tau)) \quad (2.7)$$

The fraction of the population that is susceptible and has a contact during  $J$  is

$$CS(t - \tau)d\tau \quad (2.8)$$

Hence, the fraction of the population infected during  $J$  is

$$R(t - \tau)CS(t - \tau)d\tau \quad (2.9)$$

If  $I(\tau)$  is the expected average infectiousness, as defined above, of someone infected for time  $\tau$ , then the risk due to individuals infected during  $J$  is

$$I(\tau)R(t - \tau)CS(t - \tau)d\tau \quad (2.10)$$

Note: there is an additional external risk (assumption 7) of magnitude  $a\delta(t - t_0)$ . Integrating from  $-\infty$  to  $t$  and adding the external risk gives the risk due to all individuals infected up to time  $t$

$$R(t) = a\delta(t - t_0) + \int_{-\infty}^t I(\tau)R(t - \tau)CS(t - \tau)d\tau \quad (2.11)$$

which is equivalent to Equation (2.3), by using Equation (2.7).

## 2.5 Multiple-Group Risk Model

Let  $G$  denote the number of activity groups.

8. We assume now that the number of activity groups is finite and bigger than 1.

We will include the case with an infinite number of groups by converting a sum over the activity groups to a Riemann-Stieltjes integral. Let  $C_j$  denote the number of contacts a person in group  $j$  has per unit time and  $F_j$  be the fraction of the population in group  $j$ . We claim that  $R(t)$ , the probability of a susceptible becoming infected from one contact per time unit with group  $j$  at time  $t$  is

**Proposition 2** *Assume 1-5, 7 and 8. Then  $R$  and  $A$  satisfies the system*

$$R(t) = \begin{cases} a\delta(t - t_0) + \int_{-\infty}^t I(\tau)R(t - \tau) \sum_j B_j C_j S_j(t - \tau) d\tau & \text{for } t > t_0 \\ 0 & \text{for } t < t_0 \end{cases} \quad (2.12)$$

$$A(t) = \int_{-\infty}^t R(s) ds \quad (2.13)$$

Write  $S_j(t)$  for the fraction of group  $j$  that is susceptible. Then

$$dS_j/dt = -C_j R(t) S_j \quad (2.14)$$

It follows that at time  $t - \tau$ ,

$$S_j(t - \tau) = \exp(-C_j A(t - \tau)) \quad (2.15)$$

The number of contacts the susceptible population has with group  $j$  in  $J$  is

$$C_j S_j(t - \tau) d\tau \quad (2.16)$$

If the person contacted someone from group  $j$ , then the probability that person was infected during  $J$  is

$$R(t - \tau) C_j S_j(t - \tau) d\tau \quad (2.17)$$

From the mixing assumption (assumption 3) if a person has one contact, the probability that it is with a group  $j$  person is  $B_j$ , so  $B_j$  is the weighting factor.

$$B_j = C_j F_j / \sum_i C_i F_i \quad (2.18)$$

Note,  $\sum_j B_j = 1$ .

Then the fraction of the population susceptible and having a contact during  $J$

$$\sum_j B_j C_j S_j(t - \tau) d\tau \quad (2.19)$$

Hence, the fraction of the population infected during  $J$  is

$$R(t - \tau) \sum_j B_j C_j S_j(t - \tau) d\tau \quad (2.20)$$

If  $I(\tau)$  is the expected average infectiousness, as defined above, of someone infected for time  $\tau$ , then the risk due to individuals infected during  $J$  is

$$I(\tau) R(t - \tau) \sum_j B_j C_j S_j(t - \tau) d\tau \quad (2.21)$$

Integrating from  $-\infty$  to  $t$  gives the risk due to all individuals infected up to time  $t$

$$\int_{-\infty}^t I(\tau) R(t - \tau) \sum_j B_j C_j S_j(t - \tau) d\tau \quad (2.22)$$

Adding the external risk  $a\delta(t - t_0)$  gives a total that is equivalent to Equation (2.12), by using Equation (2.15).

## 2.6 Infinitely Many Activity Groups:

From the SFCCC data we obtain 6 different activity level groups (Table 1.2), creating a step function contact rate distribution (Figure 2.4). We can view these levels or groups as an average, in reality there is a range within each group. For example, the core group (the most active group) consisted of 10% of the population with an average of 231 partners per year. Within this 10% there are those individuals who had less than 231 and those who had more. We can consider a continuous distribution that describes the population's activity levels. The mean value of the curve from 0%-10% would be 231, the average number of contacts in the core group. Similarly, the mean value of the curve from 10% to 25% would be 81, the average number of contacts for group 2, etc. Instead of considering 6 activity groups, we can consider an infinite number. Figure 2.5



gives an example of such a continuous contact distribution. Just as it would be an error to treat all individuals as having the average number of contacts, it is also an error, tho smaller, to assume there are six groups. The more groups, the less error. We now create a new model that not only allows for any infectivity distribution, but also any contact rate distribution.

*Reimann-Stieltjes Integral:* Let  $F(C)$  be the fraction of the population with activity level  $\geq C$ . If there are a finite number of activity levels, we can write

$$\sum_j C_j F_j = \int C dF(C) \quad (2.23)$$

Let  $B(C)$  be the fraction of all contacts that are with contact rate  $\geq C$ . Then if there are a finite number of groups  $B_j$  becomes  $B(C)$  where,

$$B_j = B(C) = \int_C^\infty C dF(C) / \int_0^\infty C dF(C) \quad (2.24)$$

The risk function (including the external risk) becomes

$$R(t) = a\delta(t - t_0) + \int_{-\infty}^t I(\tau)R(t - \tau) \int_0^\infty C \exp(-CA(t - \tau)) dB(C) d\tau \quad (2.25)$$

## 2.7 Numerical Solution

We can approximate Equation (2.25) by defining

$$R_\delta(t) = \begin{cases} \int_{t_0}^{t-\delta} I(\tau)R_\delta(t - \tau - \delta) \int_0^\infty C \exp(-CA_\delta(t - \tau - \delta)) dB(C) d\tau & \text{if } t > t_0 + \delta \\ a/\delta & \text{if } t \in [t_0, t_0 + \delta] \end{cases} \quad (2.26)$$

where

$$A_\delta(t) = \int_{t_0}^\infty R_\delta(s) ds \quad (2.27)$$

$A_\delta(t_0) = 0$  and  $0 < \delta \ll 1$ . We can solve Equation (2.26) incrementally on intervals  $J_n = [n\delta, (n + 1)\delta]$ . For  $t \in J_n$ ,  $R_\delta(t)$  depends only on  $R_\delta$  and  $A_\delta$  for

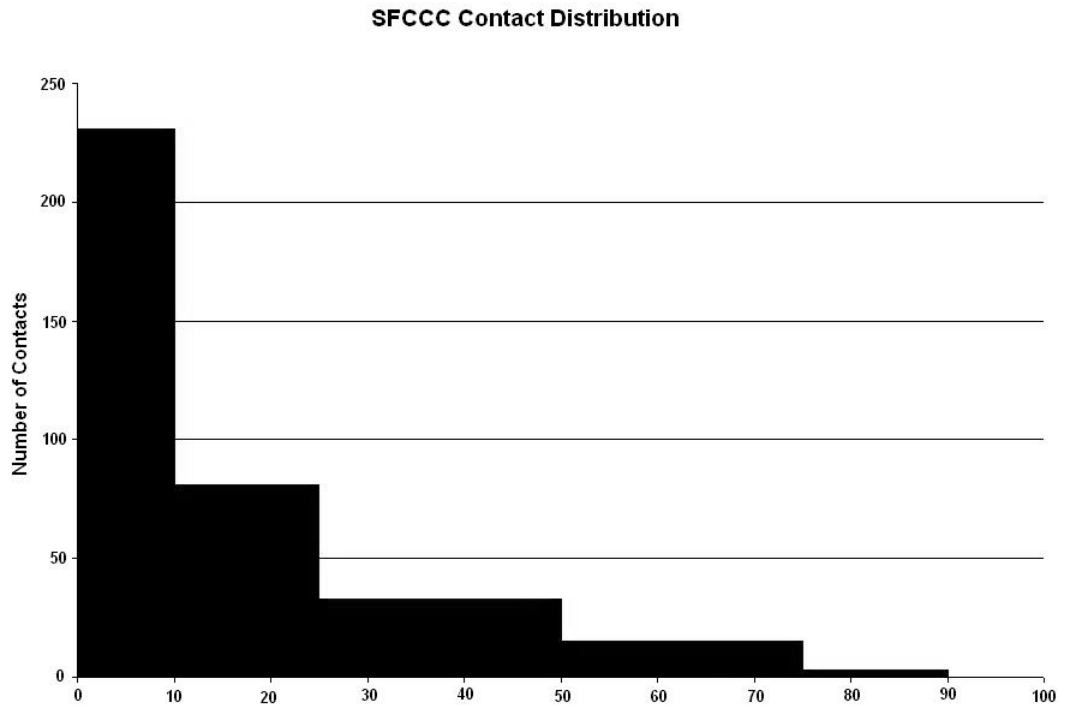


Figure 2.4: SFCCC activity levels distribution. The SFCCC reports annual numbers of partners for six different activity levels [8, 6]. Published survey data (Table 1.2, column 3) gives the distribution of the number of partners for six activity levels. The top 10% of the population “the core” has an average 231 partners per year, the next 15% of the population has an average of 81 partners per year, etc.

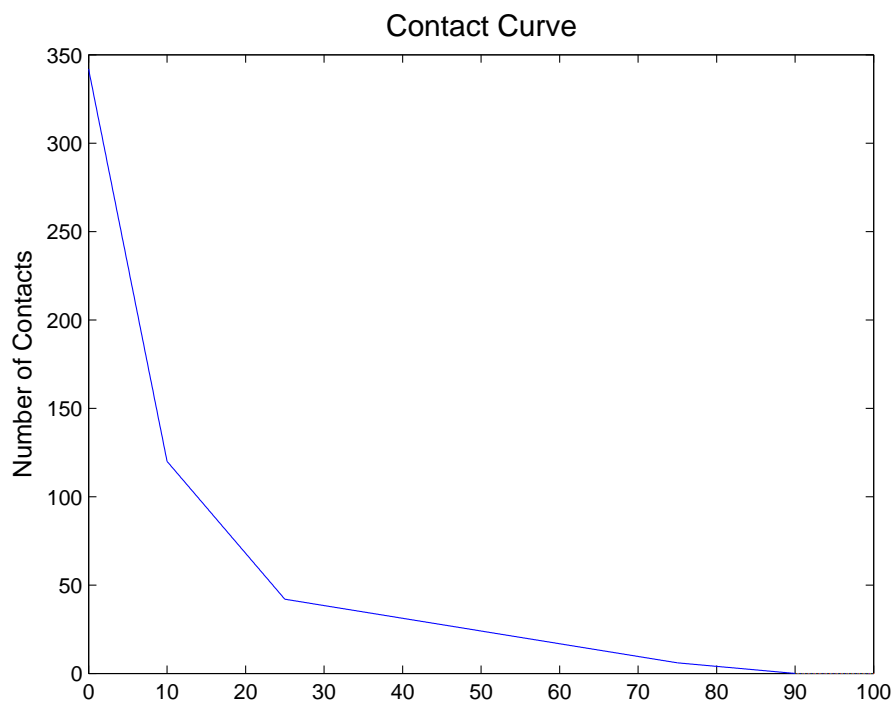


Figure 2.5: Continuous distribution describing activity levels. The mean value of the top 10% of the population has an average of 231 partners per year. This corresponds to the SFCCC survey data. The mean value of the next 15% of the population has an average of 81 partners per year, corresponding to group 2 of the SFCCC survey data.

$t \in [t_0, n\delta]$ . We use this approximation in practice with a variety of steps down to  $\delta = 1/364$  years.

## 2.8 The Distribution Problem:

Distribution problems concern allocating the relative contributions of various sources to some aggregate measure. Our distribution problem concerns partitioning the total susceptibles in the population at time  $t$  among all the activity-level groups. Many data sets have the total fraction of the population susceptible at time  $t$ , but does not allocate that fraction among the different activity levels within that population. Let  $G$  denote the number of activity groups. The case of six groups was discussed in Chapter 1, where we use a system of difference equations to show how the disease propagated through the subpopulations. Below is an alternative way of deriving the curves in Figure 1.5.

Let  $S_j(0) = 1$  (the beginning of the epidemic) where  $S_j(t)$  is the susceptible fraction of group  $j$  at time  $t$ . Write  $S'_j$  for  $dS_j/dt$ . Then

$$S'_j/S_j = R(t)C_j \tag{2.28}$$

Then

$$\ln S_j(t) = -C_j \int_0^t R(t) = -C_j A(t) \tag{2.29}$$

thus,

$$S_j(t) = \exp(-C_j A(t)) \tag{2.30}$$

Equivalently,

$$S_j(t)^{1/C_j} = \exp(-A(t)) \tag{2.31}$$

It follows that,

$$S_j(t) = S_1(t)C_j/C_1 \tag{2.32}$$

Group I (4)	Fraction $S_j = S_1 C_j / C_1$ susceptible where		
	$S_1 = 0.5$	$S_1 = 0.1$	$S_1 = 0.02$
1 ("Core")	.500	.100	.020
2	.784	.448	.254
3	.906	.720	.572
4	.956	.861	.776
5	.991	.971	.950
6	1.000	1.000	1.000
Total Pop	.882	.718	.620

Table 2.1: Group susceptible fractions (solution to distribution problem) when  $G = 6$  and number of contacts for the six groups are defined by the SFCCC data (Table 1.2).

We use this fact in Table 2.1, Columns 2-4, where we look at the case of SFCCC data where  $G = 6$  and the activity levels are defined by Table 1.2.

Initially at the beginning of the epidemic,  $t = 0$ , we have  $A(0) = 0$ , the accumulated risk function, and from then on  $A(t)$  increases, therefore  $\exp(-A(t))$  starts at 1 and decreases.

The fraction of the population susceptible is the sum of the susceptibles in each group  $j$  times the fraction of the population in group  $j$ ,

$$S(t) = \sum F_j S_j(t) = \sum F_j \exp(-C_j A(t)) \quad (2.33)$$

Ignoring  $t$  we can plot  $S$  as a function of  $\exp(-A)$  between 0 and 1 (Figure 2.6), and we obtain an increasing curve, which can be used to solve for  $A$  given any value of  $S$  between 0 and 1. Knowing  $A$  means we know each  $S_j$  by Equation

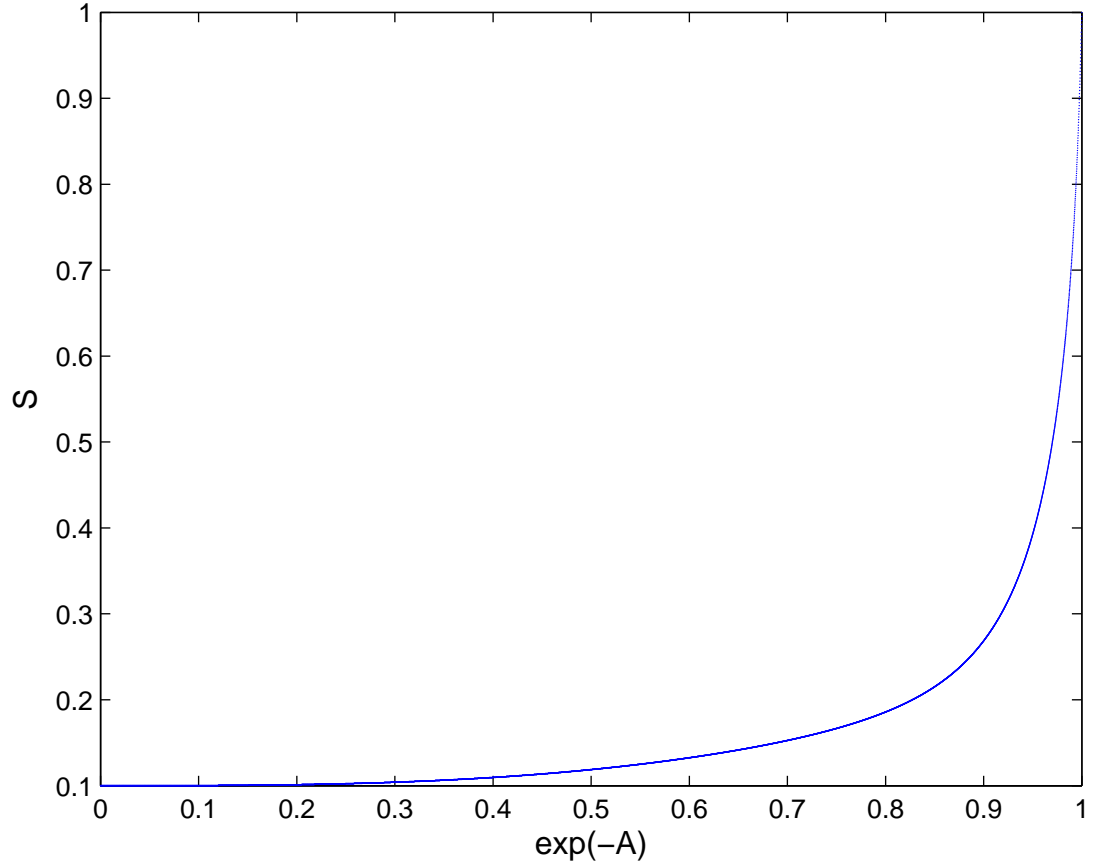


Figure 2.6: Plot of  $S(t) = \sum F_j \exp(-C_j A)$  varying  $\exp(-A)$  between 0 and 1.

2.30. Thus, from the total fraction of the population susceptible we are able to distribute them among  $G$  groups. If  $F_j^*$  denotes the fraction of the people that are in the bathhouse who are from group  $j$ , then

$$F_j^* = F_j C_j / \sum_k F_k C_k \quad (2.34)$$

It follows that for each value of  $S$ , the susceptible fraction  $S^*$  in the bathhouse is

$$S^* = \sum_j F_j S_j \quad (2.35)$$

This formula is the basis for Table 2.2, Column 2. No assumptions about contact

Year	% pop * susc. S	% susc men in bath	Num susc-inf contacts	% symp in bath	susc- symp contacts	New cases per Sus-Inf contact	Excess Cases ***	Symp infectiv- ity
1979	90.70%	74%	173	0%**	0	0.01	0	indet.
1980	79.90%	50.50%	225	0.10%	0.5	0.01	0	indet.
1981	71.20%	35%	204	0.80%	2.5	0.005	0	indet
1982	60%	23%	159	2.80%	5.8	0.02	1.63	$\geq 28\%$
1983	46%	11.80%	94	6.60%	7	0.025	1.36	$\geq 19\%$
1984	35%	6%	51	12%	6.5	0.032	1.1	$\geq 17\%$

Table 2.2: 900 Men in bathhouse on a given day \*The susceptible % of the population (Column 2) are mid-year averages from Table 1.1, Column 2, \*\* 1/6 person or less. \*\*\*Excess cases are new cases per day in excess of 1% infectivity. See Appendix D for details

infectivities are used.

## 2.9 Conclusion

We have derived a new risk model that allows for any distribution of infectiousness and an infinite number of activity level groups. Our original model, described in Chapter 1, had three levels of infectiousness corresponding to the primary, asymptomatic and symptomatic stage and the six activity levels from the SFCCC survey data. This new risk model allows much more flexibility for determining information about an infectious disease.

## Appendix A

### The Fraction of Infecteds in the Bathhouse by Activity Group

From the model equations we calculate the proportion of infected in each activity group verses time as follows:

$$I_i^t = 2 * P_i^t + L_{1,i}^t + L_{2,i}^t + L_{3,i}^t + A_i^t \quad (\text{A.1})$$

The results are shown in Figure 1.5.



## Appendix B

### Model Bookkeeping

*The model's bookkeeping of new infections in one time step:* Given the fraction in each stage of each activity group, the model computes the expected number of contacts for all of the men in each of the four stages (susceptible, primary, asymptomatic and symptomatic),  $N_{sus}, N_p, N_a,$  and  $N_s$ . Let  $I_p, I_a, I_s$  be the infectiousness per contact for the stage. The risk  $R$  of a susceptible man becoming infected from one contact is:

$$R = (I_p * N_p + I_a * N_a + I_s * N_s) / (N_{sus} + N_p + N_a + N_s) \quad (\text{B.1})$$

In each activity group, the fraction of men newly infected  $F_{new}$  at time  $t + \Delta t$  is the fraction susceptible times the number of contacts each has in time  $\Delta t$  times the risk  $R$ . To obtain the susceptible population for each activity group for the time  $t + \Delta t$ , we subtract the fraction  $F_{new}$  from the susceptible fraction for time  $t$ , and we add  $F_{new}$  to the primary stage for time  $t + \Delta t$ .

*The model's bookkeeping of the fraction in each stage:* If the average duration for a stage is  $Y$  years, then the fraction  $\Delta t/Y$  of people in that stage are moved to the next stage. We use  $2\Delta t$  years for the duration of primary stage, 7 years for asymptomatic, 3 years for symptomatic. Note on primary duration: The real meaning of the  $2\Delta t$  year primary period (which seems rather long to us) is that

people for are initially infected at time  $t$  can create new infections at time  $t + \Delta t$  and the number of contacts they have while in primary stage is  $2\Delta t$  times the number of contacts for a year. One could alternatively say the primary period is  $\Delta t$  and double the infectivity for the period.

## Appendix C

### Stochastic Model

As mentioned above, we developed a stochastic model where at each time step we first compute the fraction of people who would make each transition according to the rules of our deterministic model and convert this to a number of men by considering the late 70s-early 80s San Francisco gay population to be an estimated 70,000 individuals [31]. Using this fraction as a mean, we select a random number from a Poisson distribution. This random number becomes the number of individuals who make the transition at that time. The epidemic is then simulated repeating this Poisson process for each time step and for every transition.

Let  $f_i$  = the fraction of population in activity group  $i$ ,  $T$  =total population (70,000)

Stochastic Model

1. (a)  $P_{trans_{1,i}}^{t+1} = P_{1,i}^t$       Fraction that transition from  $P_1$  to  $P_2$  at time  $t$ 
  - (b) Let  $\lambda = P_{1,i}^t T$
  - (c) Compute random variable from 0 to 1,  $r$
  - (d) Find  $N$  such that:

$$(e) \sum_{n=0}^N \frac{e^{-\lambda} \lambda^n}{n!} = r$$

$$(f) \text{ Let } Ptrans_{1,i}^{t+1} = N/f_i/T$$

2. Repeat procedure for:

$$(a) Ptrans_{2,i}^{t+1} = P_{2,i}^t \quad \text{Fraction that transition from } P_2 \text{ to } L_1 \text{ at time } t$$

$$(b) Ltrans_{1,i}^{t+1} = \frac{L_{1,i}^t}{d} \Delta t \quad \text{Fraction that transition from } L_1 \text{ to } L_2 \text{ at time } t$$

$$(c) Ltrans_{2,i}^{t+1} = \frac{L_{2,i}^t}{d} \Delta t \quad \text{Fraction that transition from } L_2 \text{ to } L_3 \text{ at time } t$$

$$(d) Ltrans_{3,i}^{t+1} = \frac{L_{3,i}^t}{d} \Delta t \quad \text{Fraction that transition from } L_3 \text{ to } A \text{ at time } t$$

$$(e) Atrans^{t+1} = \frac{A^t}{3} \Delta t \quad \text{Fraction that transition from } A \text{ to Death at time } t$$

## Appendix D

### Table 2.2

*Lower-bound stage infectivity estimates:* We can estimate infectivity by simply assuming that symptomatic-stage HIV infectivity differs from that for primary-infection and asymptomatic stages—that is, that there are only two stage-level infectivities. In the early years of the epidemic (up through 1980), transmission was almost exclusively by primary stage men. Figure 1.4 shows negligible symptomatic-stage men in the bathhouse up through 1980 when 73.8% of the population was susceptible.

The susceptible % in the bathhouse (Column 3) is from the solution to the distribution problem as described above in Chapter 2. The number of contacts between susceptibles and infecteds (Column 4) is the product of the number of susceptibles among the 900 men<sup>1</sup>, (Column 3)  $\times$  900, and the infected proportion (100% - Column 3). For example, in 1982 when 23% were susceptible, there were 159 contacts between susceptibles and infecteds ( $= 23\% \times 900 \times (100\% - 23\%)$ ).

The symptomatic % in the bathhouse (Column 5) is the % of the population symptomatic at mid-year (Table 1.1 Column 5) times 2.5, where 2.5 is from the

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<sup>1</sup>On a typical night in 1980 approximately 900 members of the SFCCC cohort were in the bathhouse.

inverse problem solution as described above. The contacts between susceptibles and symptomatics in the bathhouse (Column 6) is the fraction of contacts between susceptibles and infecteds that involve symptomatics ( $= \text{Column 4} \times \text{Column 5}$ ). For example, in 1982 when 2.8% of the men in the bathhouse were symptomatic and there were 159 contacts between susceptibles and infecteds, there were 5.8 contacts between susceptibles and symptomatics ( $= 159 \times 2.8\%$ ).

The Number of new cases per contact between a susceptible and an infected (Column 7), which equals the number of new cases per day, is the average number of men infected daily during the year [ $= (\text{Table 1.1 Column 3 } 6875 \text{ men})/365 \text{ days}$ ] divided by the number of daily contacts between susceptibles and infecteds (Column 4). For example, in 1982 there were an average of 3.22 new infections daily [ $[(17.1\% \times 6875)/365]$ ] divided by 159 susceptible-infected contacts daily which equals 0.02 new cases per susceptible-infected contact.

We estimate symptomatic-stage infectivity (Column 9) on the basis of the excess that cannot be attributed to primary-stage transmission (Column 8). The first symptomatic AIDS cases occur in 1980. We assume that prior to 1980 pre-symptomatic (primary and asymptomatic) stage men transmitted HIV. Column 6 shows that risk being 1% per susceptible-infected contact. A lower-bound estimate on symptomatic-stage transmission risks is obtained by allocating responsibility for new infections between pre-symptomatic stage contacts at 1% risk and assigning the excess to the symptomatic stage, and then solving for symptomatic-stage transmission risks: The excess of new cases (Column 8) = New cases per day [Column 7] - (0.01 number of susceptible-infected contacts [Column 4]). The symptomatic-stage infectivity required to account for that excess [Column 9] = (excess new cases [Column 8]  $\div$  number of susceptible-infected contacts [Column

3]). For example, in 1982 we get  $3.22 - (0.01 \times 159) = 1.63$  excess new cases daily. So the infectivity required to account for those 1.63 excess new cases daily is  $163 \div 5.8 = 28\%$ .

## BIBLIOGRAPHY

- [1] A.R. Moss, D. Osmond, P. Bacchetti, J. Cherman, F. Barre-Sinoussi, J. Carlson, "Risk factors for AIDS and HIV seropositivity in homosexual men," *Amer. J. Epidemiology* **25**, 1035-1047 (1987).
- [2] D.G. Ostrow, W.J. DiFranceisco, J.S. Chmiel, D.A. Wagstaff, J. Wesch, "A case-control study of human immunodeficiency virus Type 1 seroconversion and risk-related behaviors in the Chicago MACS/CCS Cohort, 1984-1992," *Amer. J. Epidemiology* **142**, 875-883 (1995).
- [3] CDC, "Update: acquired immunodeficiency syndrome in the San Francisco cohort study, 1978-1985." *MMWR* **34**, 573-575 (1985).
- [4] H.W. Jaffe, et al., "The acquired immunodeficiency syndrome in a cohort of homosexual men: a six-year follow-up study," *Ann Intern Med* **103**, 210-214 (1985).
- [5] J.W. Curran, et al., "The epidemiology of AIDS: Current Status and Future Prospects," *Science* **229**, 1352-1357 (1985).
- [6] H.W. Hethcote and J.W. Van Ark, *Modeling HIV Transmission and AIDS in the United States* (Berlin-Heidelberg: Springer-Verlag, 1992.)



- [7] CDC, “Current Trends Update: Impact of the Expanded AIDS Surveillance Case Definition for Adolescents and Adults on Case Reporting—United States, 1993,” *MMWR* **43**, 160-161, 167-170.
- [8] D.J. Ahlgren, M.K. Gorny, A.C. Stein, “Model-Based Optimization of Infectivity parameters: A Study of the Early Epidemic in San Francisco,” *J Acqr Immune Defic Syndr* **3**, 631-643 (1990).
- [9] J.A. Yorke, N. Nathanson, G. Pianigiani, J. Martin, “Seasonality and the Requirements for Perpetuation and Eradication of Viruses in Populations,” *Am J. Epidemiol* **109**, 103-123 (1979).
- [10] G. Pantaleo, C. Graziosi, A.S. Fauci, “Review article: the immunopathogenesis of human immunodeficiency virus infection,” *N Engl J Med* **328**, 327-335 (1993).
- [11] S.J. Clark, et al., “High Titers of Cytopathic Virus in Plasma of Patients with Symptomatic Primary HIV infection,” *N Engl J Med* **324**, 954-960 (1991).
- [12] E.S. Darr, T. Moudgil, R.D. Meyer, D.D Ho, “Transient High-Levels of Viremia in Patients with Primary Human Immunodeficiency Virus Type 1 Infection,” *N Engl J Med* **324**, 961-964 (1991).
- [13] R.M. Anderson, “The spread of HIV and sexual mixing patterns,” pp. 71-86 in J. Mann and D. Tarantola (eds.), *AIDS in the World II: Global Dimensions, Social Roots, and Responses. The Global AIDS Policy Coalition* (New York: Oxford University Press, 1996).

- [14] H. Zhang, G. Dornadula, M. Beumont, L. Livornese, B. Van Uitert, K. Henning and R.J. Pomerantz, "Human Immunodeficiency Virus Type 1 in the Semen of Men Receiving Highly Active Antiretroviral Therapy," *The New England Journal of Medicine* **339**, 1803-1809 (December 17, 1998).
- [15] E.J. Bernard, "HAART and HIV Transmission," *AIDS Treatment Update*, **118**, 2-5 (October 2002).
- [16] P. Gupta, J. Mellors, L. Kingsley, S. Riddler, M.K. Singh, S. Schreiber, M. Cronin and C.R. Rinaldo, "High Viral Load in Semen of Human Immunodeficiency Virus Type 1-Infected Men at All Stages of Disease and Its Reduction by Therapy with Protease and Nonnucleoside Reverse Transcriptase Inhibitors," *Journal of Virology* **71**, 6271-6275 (August 1997).
- [17] I.M. Longini Jr., W.S. Clark, M. Haber, R. Horsburgh, Jr., "The stages of HIV infection: waiting times and infection transmission probabilities," in *Mathematical and Statistical Approaches to AIDS Epidemiology* (ed. Castillo-Chavez, C.). 110-137 (Berlin-Heidelberg: Springer Verlag, 1989).
- [18] J.A. Jacquez, J. S. Koopman, C.P. Simon, I.M. Longini Jr., "Role of the primary infection in epidemics of HIV infection in gay cohorts," *J Acqr Immune Defic Syndr* **7**, 1169-1184 (1994).
- [19] R.M. Grant and J.A. Wiley, "Infectivity of the Human Immunodeficiency Virus: Estimates from a Prospective Study of Homosexual Men," *Journal of Infectious Diseases*, **156**, 189-93 (1987).
- [20] N. Padian, S.C. Shiboski, S.O. Glass, E. Eric Vittinghoff, "Heterosexual Transmission of Human Immunodeficiency Virus (HIV) in Northern Cali-

- fornia: Results from a Ten-year Study,” *American Journal of Epidemiology* **146**, 350-57 (1997).
- [21] V. DeGruttola, G.S. Searge III, K.H. Mayer, R.C. Horseburgh Jr., “Infectiousness of HIV Between Male Homosexual Partners,” *Journal Clinical Epidemiology* **42**, 849-856 (1989).
- [22] T.A. Peterman, R.L. Stoneburner, J.R. Allen, H.W. Jaffe, J.W. Curran, “Risk of Human Immunodeficiency Virus Transmission From Heterosexual Adults with Transfusion-Associated Infections,” *JAMA* **259**, 55-58 (1988).
- [23] H.W. Hethcote and J.A. Yorke, *Gonorrhea Transmission Dynamics and Control* (Berlin: Springer-Verlag, 1984).
- [24] L.S. Doll, W. Darrow, P. O’Malley, T. Budecker, H. Jaffe, “Self-reported Behavioral Change in Homosexual Men in the San Francisco City Clinics Cohort,” III International Conference on AIDS, Washington, D.C., June 5, 1987.
- [25] CDC, “Self-Reported Changes in Sexual Behaviors Among Gay and Bisexual Men—San Francisco,” *MMWR* **34**, 613-615 (1985).
- [26] J.S. Koopman, et al., “The Role of Early HIV Infection in the Spread of HIV Through Populations,” *J Acqr Immune Defic Syndr* **14**, 249-258 (1997).
- [27] W. Winkelstein, D.M. Lyman, N. Padian, R. Grant, M. Samuel, J.A. Wiley, R.E. Anderson, W. Lang, J. Riggs, J.A. Levy, “Sexual Practices and Risk of Infection by the Human Immunodeficiency Virus: The San Francisco Men’s Health Study,” *JAMA* **257**, 321-325 (1987).

- [28] D. Werdegar, P. O'Malley, T. Bodecker, D. Echenberg, "Self-Reported Changes in Sexual Behaviors Among Homosexual and Bisexual Men from the San Francisco City Clinics Cohort," *MMWR* **36/12**, 187-189 (April 3, 1987).
- [29] E.H. Kaplan, "Modeling HIV Infectivity: Must Sex Acts be Counted?" *Journal of Acquired Immune Deficiency Syndromes* **3**, 55-61 (1990).
- [30] S.M. Blower, H.B. Gershengorn, R.M. Grant, "A Tale of Two Futures: HIV and Antiretroviral Therapy in San Francisco," *Science* **287**, 650-654 (January 28, 2000).
- [31] UNAIDS, *The evolving picture by region in Report on the global HIV/AIDS epidemic* (UNAIDS/WHO, 1998).
- [32] R. Gray, M.J. Wawer, R. Brookmeyer, N.K. Sewankambo, D. Serwadda, F. Wabwire-Mangen, T. Lutalo, X. Li, T. vanCott, T.C. Quinn and the Rakai Project Team, "Probability of HIV-1 transmission per coital act in monogamous heterosexual, HIV-1-discordant couples in Rakai, Uganda," *The Lancet* **357**, 1149-1153 (April 14, 2001).
- [33] A. Saracco, M. Musicco, A. Nicolosi, G. Angarano, C. Arici, G. Gavazzeni, P. Costigliola, S. Gafa, C. Gervasoni, R. Luzzati, F. Piccinino, F. Puppò, B. Salassa, A. Sinicco, R. Stellini, U. Tirelli, G. Turbessi, G. Vigevani, G. Visco, R. Zerboni and A. Lazzarin, "Man-to-Woman Sexual Transmission of HIV: Longitudinal Study of 343 Steady Partners of Infected Men," *JAIDS* **6**, 497-502 (1993).

- [34] M. Piatak, Jr., M.S. Saag, L.C. Yang, S.J. Clark, J.C. Kappes, K.C. Luk, B.H. Hahn, G.M. Shaw and J.D. Lifson, "High Levels of HIV-1 in Plasma During All Stages of Infection Determined by Competitive PCR," *Science* **259**, 1749-1754 (March 19, 1993).
- [35] I. De Vincenzi, "A Longitudinal Study of Human Immunodeficiency Virus Transmission By Heterosexual Partners," *The New England Journal of Medicine* **331**, 341-346 (August 11, 1994).
- [36] A. Kanabus, S. Allen, "The Origins of AIDS & HIV & the first cases of AIDS," <http://www.avert.org/origins.htm> (2004).
- [37] A.J. Nahmias, J. Weiss, X. Yao, F. Lee, R. Kodosi, M. Schanfield, T. Matthews, D. Bolognesi, D. Durack, A. Motulsky, P. Kanki, M. Essex, "Evidence for human infection with an HTLV/LAV-like virus in Central Africa, 1959," *Lancet* (i), 1279-1280 (1986).
- [38] J. Mann and D. Tarantola. "Global Overview: A powerful HIV/AIDS pandemic," pp. 5-40 in J. Mann and D. Tarantola (eds.), *AIDS in the World II: Global Dimensions, Social Roots, and Responses. The Global AIDS Policy Coalition* (New York: Oxford University Press, 1996).
- [39] CDC, "HIV incidence among young men who have sex with men—seven U.S. cities, 1994-2000," *MMWR* **50**, 440-444 (2001).
- [40] S.D. Pinkerton and P.R. Abramson, "Implications of increased infectivity in early-stage HIV Infection: application of a Bernoulli-process model of HIV infection," *Eval Rev* **20**, 516-540 (1996).

- [41] S.P. Blythe and R.M. Anderson, "Variable infectiousness in HIV transmission models," *IMA J Math Appl Med Biol* **5**, 181-200 (1988).
- [42] A.P. Bell and S. Weinburg, *Homosexualities: A Study of Diversity Among Men and Women* (Simon and Schuster, New York, 1978).
- [43] S.P. Saltzman, A.M. Stoddard, J. McClusker, M.W. Moon, K.H. Mayer, "Reliability of self-reported sexual behavior risk factors for HIV infection in homosexual men," *Public Health Reports* **102**, 692-697 (1987).
- [44] S.D. Pinkerton, P.R. Abramson, "Occasional Condom Use and HIV Risk Reduction," *Journal of Acquired Immune Deficiency and Human Retrovirology* **13**, 456-460 (1996).
- [45] H. Palacino, "Safer Sex," Chapter 10.6 in Cohen et al., *The Aids Knowledge Base*
- [46] R.M. Anderson and R.M. May, *Infectious Diseases of Humans* (Oxford University Press, 1991).