CHAPTER 6

HOMOSEXUAL MEN IN SAN FRANCISCO: SIMULATIONS AND SENSITIVITY ANALYSIS

Since homosexual men in San Francisco (SF) are probably the most studied AIDS population in the world, it is useful to demonstrate that one can simulate HIV and AIDS in this population in a manner consistent with all available information. The analysis in Chapter 5 and this chapter is important not only for a better understanding of HIV and AIDS in homosexual men in SF but also as a foundation for further work. It provides a basis for simulation modeling in later chapters of other geographic locations and other risk groups.

Chapter 3 contains the formulation of a simulation model for HIV transmission and the development of AIDS in homosexual men in SF. Here the term "homosexual men" includes bisexual men but excludes homosexual intravenous drug users. In this dynamic simulation model, the population is divided into sexually active and very active subpopulations, and the HIV incidence is proportional to the infectivity of the infected persons during their staged progression to AIDS and death. In Chapter 5 many data sources are used to estimate values or ranges of values for all parameters in the model.

Recently there has been speculation about the effects on AIDS incidence of zidovudine (ZDV), aerosol pentamidine and other forms of therapy or health care. The model is modified in Section 6.3 to include therapy for some symptomatic and AIDS patients, and data on estimated fractions of patients receiving therapy between 1987 and 1989 are presented. Parameter sets and simulations consistent with therapy fractions are compared to the baseline parameter set and simulations. Comparisons suggest the relative influences on AIDS incidences of saturation in the high–risk group, changes in sexual behavior, and therapy.

The simulation modeling approach to the HIV epidemic in homosexual men in SF has been used previously. Pickering et al. (1986) used a discrete time, nonlinear model for sexual transmission of HIV with several possible courses of infection and used reported anal–rectal gonorrhea data to estimate the changes in homosexual behavior. They analyzed and forecast AIDS incidence in homosexual men in three cities including SF, but they concluded that there was insufficient data before 1986 to choose between radically different forecasts. Ahlgren et al. (1990) developed a dynamic transmission model and found parameter values which optimized the fit to the seroconversion data from the SF Vaccine Trial Cohort and AIDS incidence in homosexual men in SF for 1978 to 1986. Their modeling experiments suggested that the high infectivity of the short–lived, antigen–bearing first stage of HIV infection may have caused the rapid rise in the early epidemic in SF. Direct projections of AIDS incidence can be made by using an HIV seroincidence curve and a distribution for the AIDS incubation period, but this method yields no information on HIV transmission. This approach has been used in SF by Lemp et al. (1990).

The simulation modeling approach used here yields an HIV transmission dynamics model with parameter estimates. The major emphasis in this analysis is to obtain *a priori* parameter estimates from multiple sources and then to see if all of these parameter estimates are consistent in a simulation model with estimated HIV and AIDS incidences. Thus the goal is not to provide

AIDS incidence forecasts but to provide a dynamic simulation model with parameter values which reconstructs what has occurred up to the present. The primary limitation of our modeling is that the model is only a simple approximation of reality; moreover, it is not possible in this model which simulates transmission dynamics to estimate the deviations of the model simulations from reality. When interpreting modeling results, one must be aware of the approximations involved in the formulation of the model. Further discussion of the purposes and limitations of epidemiologic modeling is given in Section 1.6.

6.1 The Fit Criteria

The first fit criterion for the simulations is that the parameter values must be close to the parameter estimates obtained in the Chapter 5. The second criterion is that the HIV and AIDS incidence in the simulations must be close to the estimated HIV and AIDS incidence values given in Table 5.1. The goodness of fit is measured by the chi-square (χ^2) statistic, i.e., the sum of the squares of the observed values minus the expected values of the incidences divided by the expected values. The quantity minimized in the fitting procedure is the sum of 0.02 times the χ^2 value for the HIV incidences and 0.98 times the χ^2 value for the AIDS incidences. These weights are chosen so that the two contributions to the minimized quantity are of the same magnitude.

In Table 6.1 the most reliable parameter values have been fixed at values equal to their listed *a priori* estimates. Values for the starting and stopping dates and initial estimates for the other three optimization parameters have been entered into a computer program that varies η, PAS and RDN in order to minimize the weighted sum of the χ^2 values. The six optimization parameters (see Table 6.1) whose values and simulation best satisfy the fit criteria have been found by comparing computer runs. The sensitivity to changes in the fixed and optimization parameters is considered in Section 6.4.

6.2 The Baseline Parameter Set

6.2.1 Simulation Results

The effects of changes in parameters have been explored by using a "baseline parameter set." Table 6.1 gives the baseline parameter set, and Table 6.2 and Figure 5.1 give the corresponding simulation results. In Table 6.1 the fixed parameter values are equal to their *a priori* estimates in Chapter 5. The optimization parameters which give the best fit in the sense of minimizing the weighted sum of the χ^2 values are consistent with the *a priori* estimates. The epidemic starting date is October 1975, and the external mixing fraction is 0.82. Decreases in homosexual partnership rates occur each month between August 1981 and December 1986 with a yearly reduction factor of 0.61. Note that these values are consistent with the *a priori* estimates that the reduction occurred for several years starting around 1982 with a yearly reduction factor in the interval (0.4, 0.7). The average number PAS of partners per month before reduction is 0.75, which is less than the *a priori* estimate of 2, but in the model PAS is multiplied by QH,

Table 6.1 Baseline parameter set

Fixed Parameters	
Population size	$Q = 56{,}000$
Natural mortality rate constant	$\mu = 0.000532$
Monthly migration percentage	$\delta = 0.05/12$
Monthly activity level change rate constant	$\phi = 0.05/12$
Probability of transmission	$QH = 0.05$
Mean times in phases	2.2, 52.6, 62.9, and 18.0 months
Very active fraction	$F = 0.10$
Activity level ratio	$R = 10$
Relative weights ($\omega \times \rho$) of transmission in 4 phases	2, 1, 1.5, and 7.5
Number of stages	$m = 7$
Optimization Parameters	
Starting date of the epidemic	STD = October 1975
Reduction starting date	STR = August 1981
Reduction stopping date	STP = December 1986
External mixing fraction	$\eta = 0.82$
Average number of partners per month before STR	PAS = 0.75
Yearly reduction factor	RDN = 0.61

the probability of transmission per partner. If QH were changed from 0.05 to 0.019, then PAS would change from 0.75 to 2.0, the *a priori* estimate. In the baseline parameter set, the average time between new sex partners before reduction starts is 0.25 months for very active men and 2.5 months for active men. After reduction by a factor of about 0.07 through December 1986, the average time between new partners is 3.5 months for very active men and 35 months for active men.

Figure 5.1 and Table 6.2 show that the HIV incidences before 1985 in the simulation follow the general pattern of the estimated HIV incidences of Bacchetti (1990), but are usually above those estimates. Bacchetti obtained his estimates by using a scaling factor to match his HIV prevalence estimate of 20,060 in September 1984; if his scaling factor were increased by only 10%, then the HIV simulation curve would be closer to his estimates. As seen in Table 6.2, the HIV incidences after 1986 in the simulations are close to the estimates of 720 per year. The HIV prevalence of approximately 18,700 in 1984 is close to the cumulative HIV incidence of 20,060 by September 1984 obtained by Bacchetti (1990). The fit of the simulated AIDS incidence to the estimated AIDS incidence is quite good. Lang et al. (1991) estimated that there were 2381 living

Table 6.2 Simulation results for parameters in Table 6.1.

YEAR	YEARLY HIV INCIDENCE EST*	SIM+	HIV PREV	PREVALENCE+ FRACTIONAL PREV ALL	V_A	ACT	YEARLY AIDS RESULTS INCIDENCE EST*	SIM+	AIDS PREV+	AIDS DEATHS	AIDS OUTSIDE SF
1975	*****	1.	2.	.00	.00	.00	*****	0.	0.	0.	0.
1976	*****	15.	17.	.00	.00	.00	*****	0.	0.	0.	0.
1977	*****	84.	98.	.00	.01	.00	*****	0.	0.	0.	0.
1978	439	469.	553.	.01	.06	.00	0	0.	0.	0.	0.
1979	1963	2162.	2642.	.05	.26	.02	0	1.	1.	0.	0.
1980	4390	5489.	7859.	.14	.66	.08	2	4.	4.	1.	0.
1981	5721	6284.	13538.	.24	.87	.17	22	21.	19.	6.	3.
1982	4337	4021.	16680.	.30	.90	.23	86	78.	72.	25.	11.
1983	2362	2562.	18178.	.32	.88	.26	228	213.	203.	81.	38.
1984	1269	1709.	18656.	.33	.85	.28	442	437.	441.	199.	94.
1985	762	1161.	18401.	.33	.79	.28	678	717.	774.	384.	185.
1986	720	788.	17583.	.31	.73	.27	1010	997.	1152.	619.	306.
1987	720	686.	16488.	.29	.66	.25	1275	1226.	1513.	865.	439.
1988	720	733.	15305.	.27	.60	.24	1285	1370.	1802.	1082.	565.
1989	720	758.	14073.	.25	.55	.22	1338	1424.	1986.	1240.	667.
1990	720	761.	12839.	.23	.50	.20	1551	1399.	2058.	1327.	735.
1991	*****	746.	11649.	.21	.46	.18	*****	1316.	2031.	1343.	767.
1992	*****	718.	10541.	.19	.43	.16	*****	1201.	1930.	1302.	766.
1993	*****	683.	9537.	.17	.40	.15	*****	1074.	1784.	1221.	739.
1994	*****	644.	8646.	.15	.37	.13	*****	950.	1617.	1117.	694.
1995	*****	606.	7868.	.14	.35	.12	*****	838.	1448.	1007.	640.

*These are the estimated (EST) values in Table 5.1.
+These are the values from the simulation (SIM) model; V_A means very active, ACT means active, PREV means prevalence, and
OUTSIDE SF is the AIDS incidence outside San Francisco.

AIDS cases in SF in October 1989. Since 85% of AIDS cases in SF in 1989 were in homosexual/bisexual men, their estimate yields 2024 as the AIDS prevalence in homosexual men in 1989, which is close to the prevalence of 1986 in the simulation in Table 6.2. The weighted sum of the χ^2 values of the HIV incidences (594) and the AIDS incidences (35.4) is 46.6.

Certain patterns can be seen in Table 6.2 and Figure 5.1. The peak AIDS incidence in 1989 occurs 5 years after the peak in HIV prevalence in 1984 and 8 years after the peak HIV incidence in 1981. The peak in AIDS deaths occurs about 1 year after the peak in AIDS incidence. The eight–year delay between the peaks in HIV incidence and AIDS incidence is reasonable, since the median incubation period for the seven–stage progression model is 9.6 years. This reinforces the concept that a change in HIV incidence (such as a peak) can cause a similar change many years later in AIDS incidence.

Saturation in the very active group can be seen in Table 6.2. The fractional HIV prevalence in the very active group reaches a peak of 90% infected in 1982, about 1 year before the overall fractional prevalence peak of 33% and about 2 years before the peak prevalence of 28% in the active group. The increase in the HIV prevalence in the very active group between 1979 and 1981 is very dramatic. In the early years, nearly everyone with AIDS was in the very active group, but by 1988, the percentage of those with AIDS who were very active was 26% (value not given in Table 6.2). The large number of homosexual men who were infected with HIV while living in SF but developed AIDS after they left is shown in Table 6.2. Although the migration rate is only 5% per year in the simulation, the AIDS incidence in former SF residents is 53% of the AIDS incidence in SF residents in 1990.

6.2.2 Calculations of the Contact Number

It is interesting to calculate the *spectral radius* ρ of the matrix T given in Section 4.5 using parameter values corresponding to the baseline parameter set in Table 6.1. Recall from Chapter 4 that the spectral radius $\rho(T)$ is the contact number (reproduction number) for the difference equation model used here, so it determines whether the disease dies out ($\rho(T) \leq 1$) or remains endemic ($\rho(T) > 1$). In this model with the average number of new sexual partners per month given by $PAS = 0.75$, corresponding to the situation before any behavioral changes, the average number of new partners per month is 3.95 for people in the very active group and 0.395 for people in the active group. In this case, the spectral radius is found numerically using MATLAB to be $\rho(T) = 1.32$. This means that the average HIV–infected person has a contact sufficient for transmission with 1.32 persons during the average infectious period (about 10 years in length). It also means that at the endemic equilibrium, the HIV–infected fractional prevalence would be $1 - 1/\rho(T) = 0.24$ if the population were homogeneous. Of course, the population model is not homogeneous so the equilibrium HIV fractional prevalence is higher than 0.24 in the very active group and lower in the active group.

Using the yearly reduction factor $RDN = 0.61$ in Table 6.1 for the reduction time period of 5 years and 5 months reduces PAS from 0.75 to 0.0516, which changes $\rho(T)$ to 1.0091. Even though PAS has been reduced by a factor of 15, the disease persists since $\rho(T)$ is still

above the threshold of 1. In order to get the spectral radius below 1, PAS must be below 0.03 so PAS must be reduced by another factor of about 1.7 in order to get below the threshold. Of course, if PAS is barely below 0.03, then $\rho(T)$ would be barely below 1 and HIV would die out very slowly. For example, if $\rho(T) = 0.99$, then it would take 69 ten–year intervals for the number of cases to decrease by half. It is important to realize that the modeling results are insensitive to the reduction stopping date, so the fit to the HIV and AIDS incidence data is almost as good if the yearly reduction with RDN = 0.61 did not stop in December 1986, but continued through 1990. In this case PAS would now be below 0.03 and the spectral radius $\rho(T)$ would be below 1 so that the HIV epidemic would be dying out. The significant conclusion is that we cannot determine from the modeling or the data whether $\rho(T)$ is now above or below the threshold, i.e., whether the HIV epidemic is now persisting or is slowly dying out.

It is surprising that a reduction in PAS, the average number of new partners per month, by a factor of 15 only decreases the spectral radius by a factor of about 1.3 from 1.32 to 1.0091. Moreover, PAS must be reduced by a factor of about 25 from 0.75 to 0.03 in order to get the spectral radius $\rho(T)$ reduced from 1.32 to 1.0. It seems plausible that the low responsiveness of the spectral radius to changes in the partnership rate PAS is due to factors such as the very long infectious period for HIV infecteds or the ability of HIV to persist in the "core" population of very active homosexual men.

6.3 Modeling Zidovudine Therapy

Recently there has been great interest in the possible effects on AIDS incidence of the treatment of some patients with zidovudine (ZDV) and the use of PCP prophylaxis (usually aerosol pentamidine) (Gail et al., 1990). The simulation model has been modified to include therapy; here therapy primarily refers to ZDV treatments, but it also includes aerosol pentamidine, other drugs, and other recent improvements in health care. Estimates of the fractions of HIV–positive homosexual men in SF receiving therapy are given for recent years, and simulations which satisfy the fit criteria and fit the therapy data are found.

6.3.1 Modification of the Simulation Model to Include Therapy

The simulation model is modified to include therapy by creating a separate track for treated people in the final symptomatic stage and in the AIDS stage, with longer mean residence times in these treated compartments. The final symptomatic stage (stage 6 if $m = 7$) with mean residence time of 1.7 years corresponds closely to a symptomatic stage with CD4 cell count below 200 cells/ml, which has a mean residence time of 1.6 years (see Chapter 2). The new parameters in the model are: 1) the monthly rate constants TF6 and TFA for moving stage 6 and AIDS patients into the treated track, 2) the starting dates ST6 and STA for the treatment of stage 6 and AIDS patients and 3) the multiplying factor TP of the transfer rate constants for the treated stages. Thus, TP = 0.5 means that the transfer rate constant is halved for the treated patients, so that the mean time in the stages is doubled for treated patients.

6.3.2 Estimates of the Therapy Percentages and Effects

Using data from the SF Men's Health Study and the SF General Hospital Cohort, Lang et al. (1991) have estimated that the percentages of homosexual men with AIDS in SF receiving ZDV were 36% in 1987, 54% in 1988, and 58% in 1989. They also estimated that the percentages of HIV–positive homosexual men in SF with CD4 count below 200 (but without AIDS) receiving treatment were 24% in 1987, 55% in 1988, and 52% in 1989. For HIV positive homosexual men in SF with CD4 count between 200 and 499, the percentages receiving ZDV were estimated to be 1% in 1987, 10% in 1988, and 16% in 1989. Andrews et al. (1990) report that ZDV was primarily available to AIDS patients after it had been officially approved on March 24, 1987, and became broadly available on September 15, 1987. Thus initial estimates for the starting dates for ZDV therapy are STA = April 1987 and ST6 = October 1987.

Zidovudine therapy lengthens the survival time of AIDS patients and slows progression to AIDS for HIV–positive symptomatic individuals. Gail et al. (1990) used relative risk factors of 0.5 or 0.33, which correspond to doubling or tripling the mean progression and survival times. Lemp (1990) recently surveyed reports on the effects of therapy on AIDS survival, and although there are many different measures of the effectiveness of ZDV therapies, they seem to be roughly consistent with doubling the mean time in the AIDS stage or in stage 6, which corresponds to a transfer rate multiplying factor of TP = 0.5.

6.3.3 Simulations Including Therapy

The therapy information above imposes two additional fit criteria. The first is that the percentages of AIDS patients treated in the simulation are close to the estimated 36%, 54%, and 58% in 1987, 1988, and 1989, respectively. The starting date STA and transfer rate constant TFA for treated AIDS patients are adjusted to achieve this. The second additional fit criterion is that the percentages of stage 6 men treated in the simulations are close to the estimated 24%, 55% and 52% in 1987, 1988 and 1989, respectively. In this case the starting date ST6 and transfer rate constant TF6 for therapy of stage 6 patients are adjusted. The small percentages of men with CD4 counts between 200 and 499 who received ZDV are ignored; they would have almost no influence on AIDS incidence through 1990. The transfer rate multiplying factor TP for stage 6 and the AIDS stage is equal to the *a priori* estimate of 0.5 which corresponds to doubling the mean residence times for treated patients.

The fixed parameters in Table 6.1 are used in the simulations with therapy. For TP = 0.5, STA = April 1987, and ST6 = October 1987, the transfer rate constant values TFA = 0.05 and TF6 = 0.05 give treatment percentages consistent with the *a priori* estimates. Transfer rate constants TFA = 0.025 and TF6 = 0.025 give treatment percentages which are about half of the *a priori* estimates. The simulation results for the best fit using these parameters is given in Table 6.3. Most of the parameter values corresponding to Table 6.3 are similar to those in Table 6.1. The epidemic starting date STD is July 1975 and the external mixing fraction η is 0.82. The average number PAS of partners before reduction is 0.71, the yearly reduction factor RDN is 0.57, reduction starts in April 1982 and ends in December 1986.

Table 6.3 Simulation results with therapy transfer constant of 0.025.

YEAR	YEARLY HIV INCIDENCE EST*	YEARLY HIV INCIDENCE SIM+	HIV PREV	YEARLY AIDS INCIDENCE EST*	YEARLY AIDS INCIDENCE SIM+	TREATMENT+ STAGE 6 TREATED	STAGE 6 %	AIDS TREATED	AIDS %
1975	*****	3.	4.	*****	0.	0.	0.	0.	0.
1976	*****	19.	22.	*****	0.	0.	0.	0.	0.
1977	*****	101.	121.	*****	0.	0.	0.	0.	0.
1978	439	512.	616.	0	0.	0.	0.	0.	0.
1979	1963	2143.	2683.	0	1.	0.	0.	0.	0.
1980	4390	5146.	7561.	2	5.	0.	0.	0.	0.
1981	5721	6227.	13208.	22	22.	0.	0.	0.	0.
1982	4337	5146.	17460.	86	79.	0.	0.	0.	0.
1983	2362	3084.	19423.	228	210.	0.	0.	0.	0.
1984	1269	1936.	20054.	442	433.	0.	0.	0.	0.
1985	762	1246.	19806.	678	722.	0.	0.	0.	0.
1986	720	806.	18921.	1010	1023.	0.	0.	0.	0.
1987	720	689.	17758.	1275	1275.	173.	7.	249.	17.
1988	720	746.	16589.	1285	1352.	690.	25.	592.	32.
1989	720	783.	15448.	1338	1374.	1014.	34.	908.	44.
1990	720	805.	14347.	1551	1360.	1204.	40.	1164.	52.
1991	*****	813.	13299.	*****	1301.	1294.	45.	1349.	58.
1992	*****	808.	12317.	*****	1209.	1308.	48.	1462.	62.
1993	*****	793.	11414.	*****	1101.	1270.	51.	1509.	66.
1994	*****	771.	10596.	*****	991.	1200.	53.	1503.	69.
1995	*****	745.	9863.	*****	889.	1113.	54.	1457.	71.

*These are the estimated (EST) values in Table 5.1.
+These values are from the simulation (SIM) model.

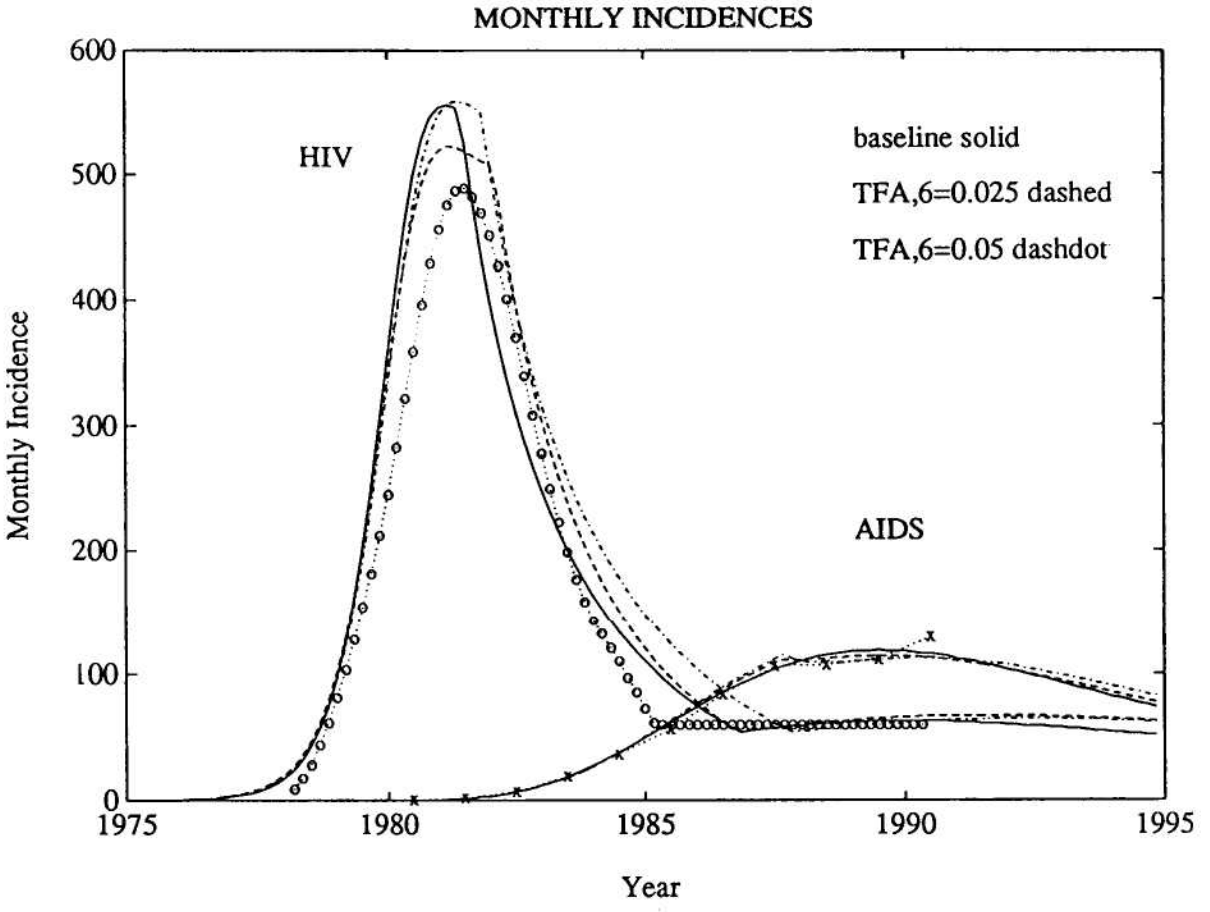

Figure 6.1 The best–fitting simulations with therapy are shown for therapy transfer constants of 0.025 and 0.05.

Figure 6.1 shows the simulation results for the best fits with the two sets of transfer rate constants. Although the two HIV incidence curves in Figure 6.1 are above the estimated curve, they give as good a fit to the estimated HIV incidence curve as the baseline parameters. The estimated AIDS incidence curve is best fit by the baseline parameter set (weighted $\chi^2 = 47$), adequately by the TFA = TF6 = 0.025 curves ($\chi^2 = 52$) and slightly worse by TFA = TF6 = 0.05 curves ($\chi^2 = 73$.) None of the three AIDS incidence curves match the 1990 AIDS incidence data. The better fits with half the estimated percentages treated suggest that the estimates of Lang et al. (1991) on the percentages in SF receiving ZDV therapy from 1987 to 1989 could be too large, possibly because the samples in the cohorts used for the estimates may not have been representative of all homosexual men in SF.

Thus the simulations with and without therapy all give adequate fits to the HIV and AIDS incidences. If the AIDS incidence in 1990 is ignored, then the models with therapy give a better fit, since they have a plateau in AIDS cases between 1987 and 1989 consistent with the data. Since all simulations with and without therapy give adequate fits, it is not possible to determine the importance of therapy from the model at this time.

Table 6.4. Sensitivity summary for parameters in Table 6.1

Parameter	Sensitivity
Q	relatively insensitive when Q is increased or decreased by 30–40%.
μ	imperceptible changes when μ is zero or doubled.
δ	somewhat sensitive to δ as seen in Figure 6.2.
ϕ	insensitive when ϕ is halved or doubled.
QH	sensitivity is the same as for PAS below.
γ_i	not very sensitive to scaling up or down by 10% as seen in Figure 6.4.
F & R	not very sensitive to halving or doubling F and R.
$\omega_i\rho_i$	fits with a wide variety of weights of transmission are possible.
m	somewhat sensitive to m as seen in Figure 6.3.
STD	insensitive to 6 month changes.
STR	insensitive to 3 month changes.
STP	insensitive to 6 month changes.
η	not sensitive for $0.50 \leq \eta \leq 1$, but sensitive for small η.
PAS	somewhat sensitive to 10% changes.
RDN	relatively insensitive to 10% changes.

6.4 Sensitivity Analysis

A dynamic model is said to be sensitive to a parameter if small changes in the parameter value have a big effect on the outcome, and insensitive to a parameter if small changes in the parameter value have little effect. In this section, all parameters are assumed to be equal to those in the baseline parameter set in Table 6.1 unless otherwise specified. Table 6.4 summarizes the sensitivity results described below.

6.4.1 Population Structure and Dynamics

When the best–fitting simulations have been found for a population size Q of 40,000, the HIV incidence curve is wider and lower than for the baseline parameter set, but the AIDS incidence curve is very similar. When the population size Q is changed to 80,000, both the HIV and AIDS incidence curves for the best–fitting simulation are similar to those for the baseline parameter set. Thus the simulations are relatively insensitive to the population size Q. The simulations are also insensitive to the mortality rate constant μ since changes are imperceptible when μ is halved or doubled.

Changing the yearly migration rate δ from 5% of the population to other values such as 0%, 3%, and 8% does cause changes in the best–fitting simulations for both the HIV and AIDS incidence curves, as shown in Figure 6.2. The AIDS incidence in 1995 is 57% higher when δ is 0% than when δ is 8%. The explanation is that with the larger values of δ, many of those infected in SF emigrate before they are diagnosed with AIDS, so the number of SF residents diagnosed with AIDS in 1995 is lower.

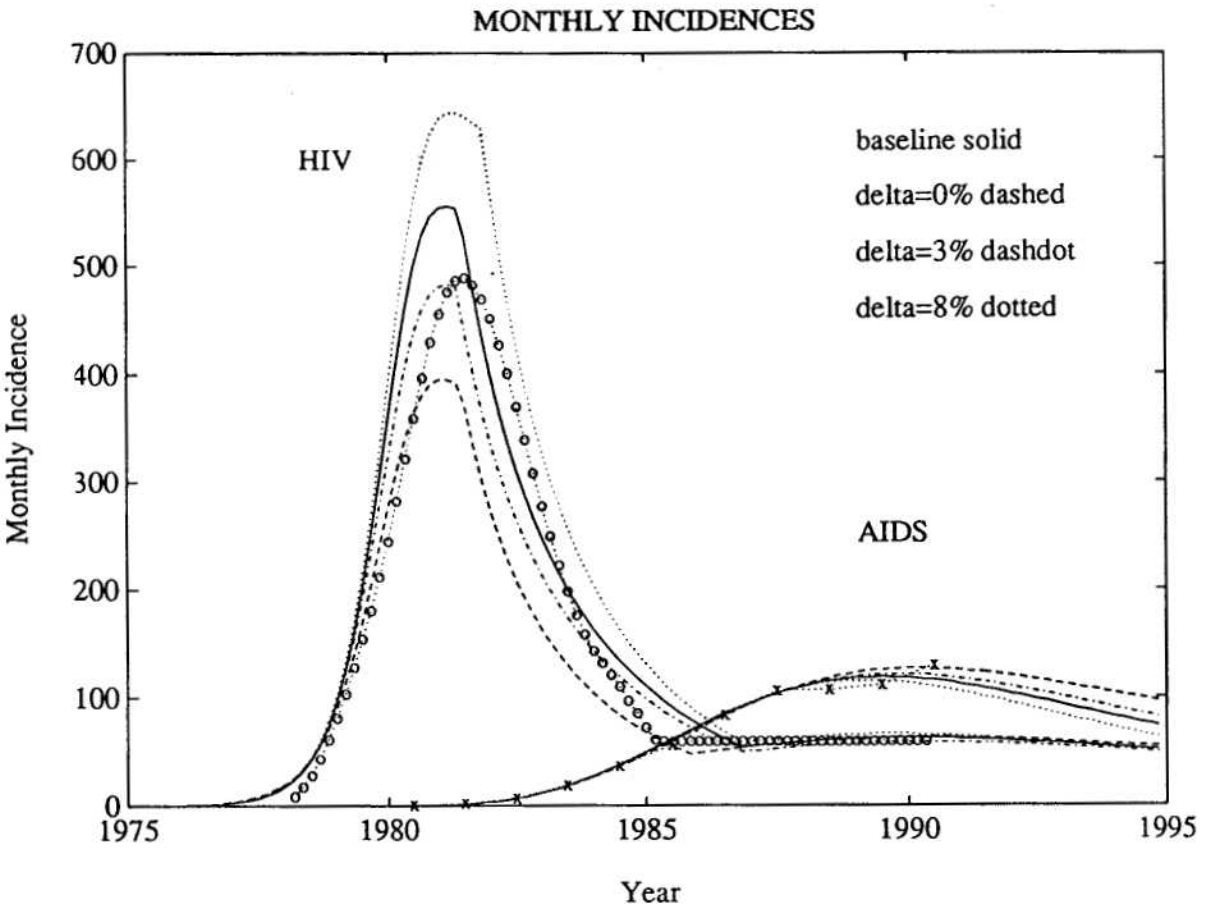

Figure 6.2. The best–fitting simulations are shown where the yearly migration rate δ is 5% (baseline), 0%, 3%, and 8%.

6.4.2 Epidemiological Structure and Mixing

The two parameters that define the activity structure are the very active fraction F and the activity level ratio R. The *a priori* baseline values for them are $F = 0.1$ and $R = 10$, so that 10% of the population is ten times as active. Halving or doubling F with R fixed at 10 leads to only minor changes in the best–fitting simulation. Halving or doubling R with F fixed at 0.1 also leads to minor changes. Doubling F to 0.2 and halving R to 5 leads to only minor changes. Changes in the activity level transfer rate constant ϕ away from the baseline value of 5% transfer per year cause imperceptible changes in the best–fitting simulations. Since the simulated HIV incidence curves are reasonably close to the estimated HIV curve and the simulated AIDS incidence curves are essentially the same for all of these changes in F, R, and ϕ, the simulation modeling is relatively insensitive to changes in these parameters.

Homogeneous mixing with no activity levels corresponds to $R = 1$. A best– fitting simulation with $R = 1$ has HIV and AIDS incidence curves which are similar to the estimated incidence curves. For $R = 1$ this best fit has STD = January 1976, STR = April 1979, STP = December 1986, PAS = 2.8, RDN = 0.61, and $\eta = 1$. All of these are consistent with the *a priori* estimates except the starting year STR for the reduction in the average number of partners per month, which is at least 2 years earlier than the *a priori* estimate. This best fitting simulation is not allowable since the STR value is unrealistic. The best fit with STR values in 1981 or 1982

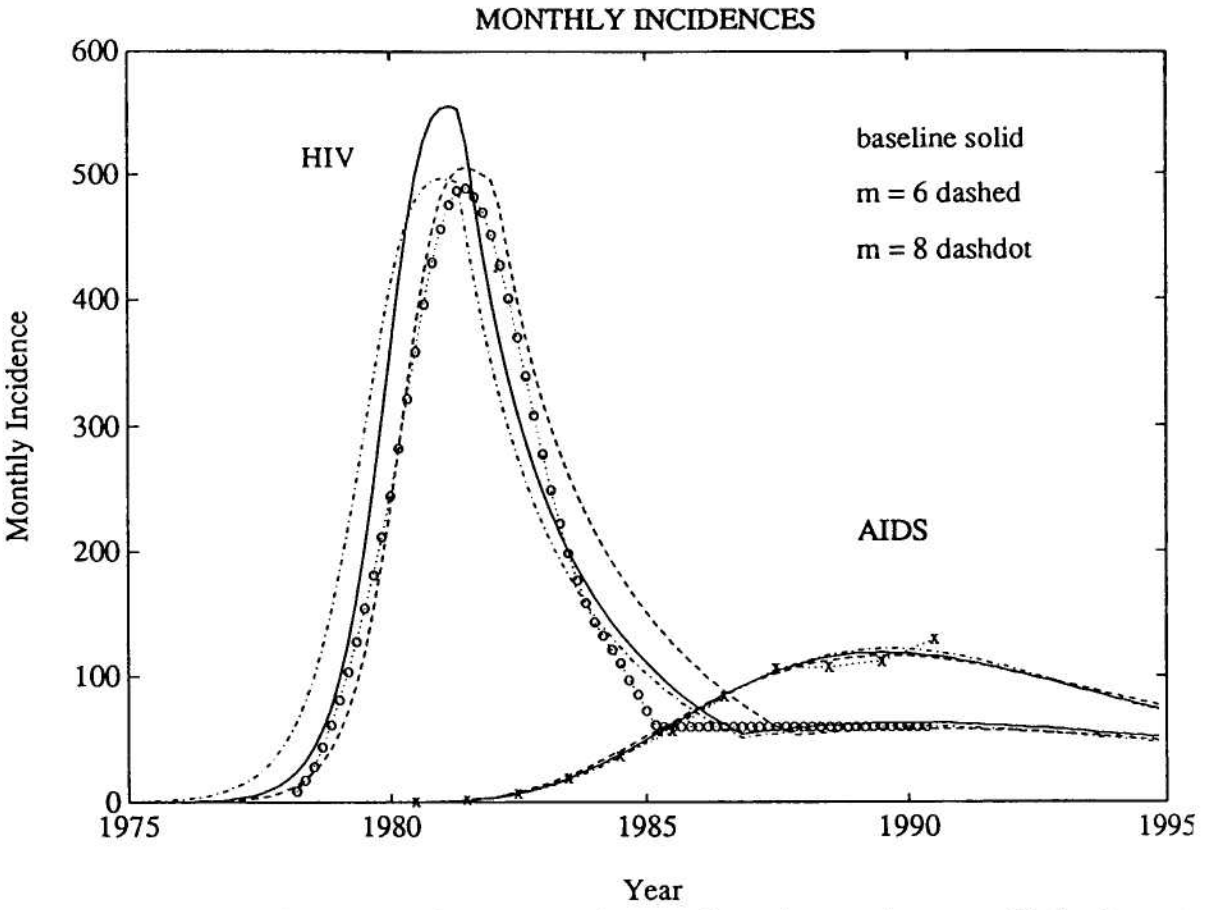

Figure 6.3 The best–fitting simulations are shown where the number m of infectious stages is 7 (baseline), 6, and 8.

does not give an adequate fit ($\chi^2 > 500.$) Thus homogeneous mixing with R = 1 is not adequate so that there must be two sexual activity levels.

The external mixing fraction η is 0.82 in the baseline parameter set in Table 6.1, which means that the mixing pattern between people in the activity levels is quite close to the standard proportionate mixing corresponding to $\eta = 1$. Changing η to 1, 0.9, or 0.75 and varying PAS and RDN to give the best fits yields simulations with HIV incidence curves similar to that of the baseline and AIDS incidence curves almost identical to that of the baseline. Thus the simulations are not very sensitive to η near 0.82, but they are sensitive to η when η is near zero, which corresponds to uncoupling the sexual activity levels. Choosing $\eta = 1$ reduces the number of parameters by one since this corresponds to assuming that the sexual partnership formation is governed by the proportionate mixing assumption as defined in Chapter 3.

The epidemic starting date STD is October 1975 in the baseline parameter set. If this starting date is shifted by six months earlier or later, the best–fitting simulations are only slightly different from the baseline simulations. Thus the simulation modeling is relatively insensitive to changes in the epidemic starting date.

6.4.3 Parameters Related to the Stages

The best–fitting simulation curves when the number m of infectious stages is 6, 7, or 8 are shown in Figure 6.3. Although the HIV incidence curves are somewhat different, the AIDS

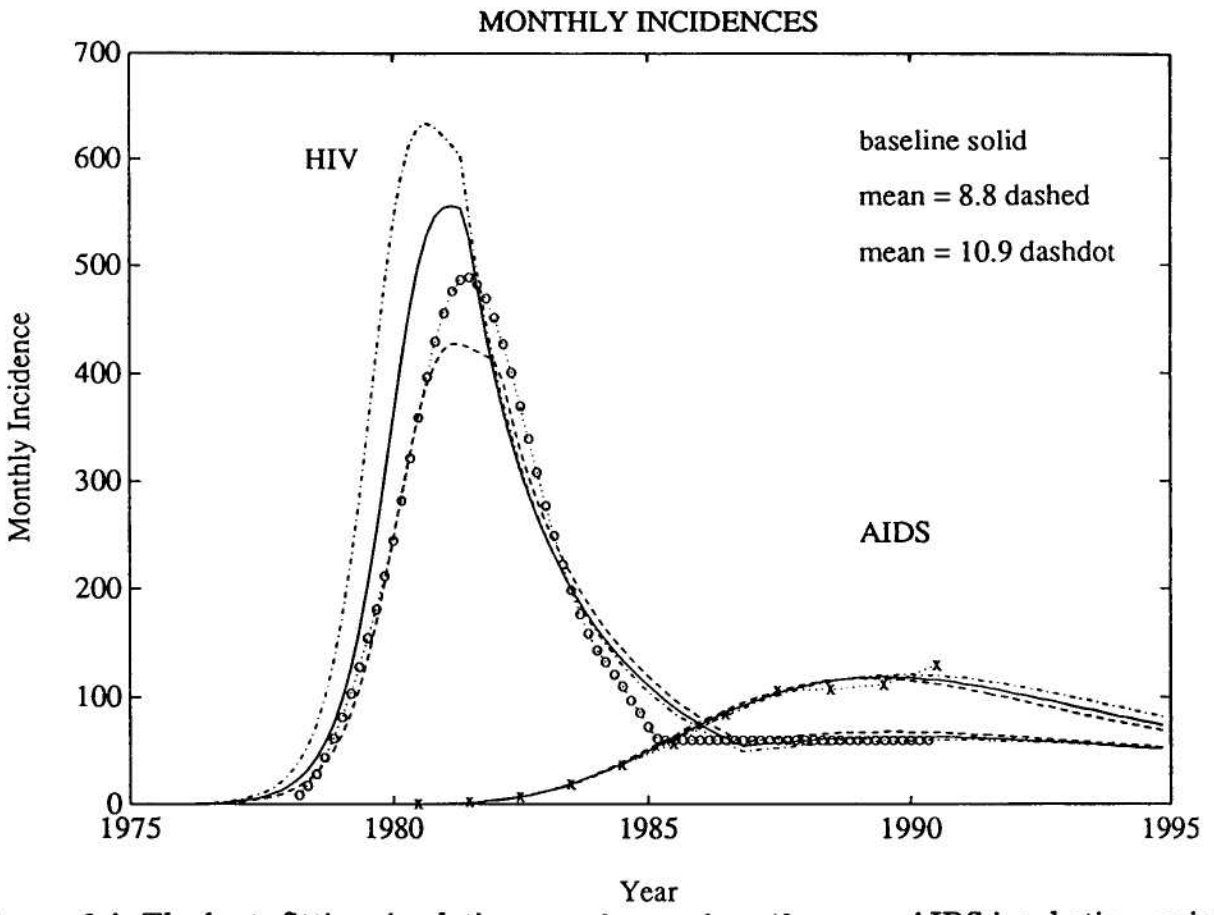

Figure 6.4 The best–fitting simulations are shown where the mean AIDS incubation period is 9.8 years (baseline), 8.8 years, and 10.9 years.

incidence curves are very similar. The $m = 7$ curves correspond to the baseline parameter set. For $m = 6$, the optimization parameters are STD = January 1976, $\eta = 0.75$, PAS = 0.70, RDN = 0.63, STR = April 1982, and STP = December 1987; these are all consistent with the *a priori* estimates. For $m = 8$, the epidemic starting date of July 1974 is early but plausible; the other optimization parameters are consistent with the *a priori* estimates.

Best–fitting simulations have been found when the mean incubation period is 8.8 years = (9/10) × 9.8 years, so that the baseline rate constants γ_i for progression between the stages are all multiplied by a 10/9 factor. Best fits have also been found when the mean incubation period is 10.9 years = (10/9) × 9.8 years so that the baseline γ_i values are all multiplied by 9/10. As seen in Figure 6.4, the HIV incidence simulation curve corresponding to a mean of 8.8 years is close to the estimated HIV curve, but the simulation curve corresponding to a mean of 10.9 years is not as close. However, the HIV curves for means of 8.8, 9.8, and 10.9 years are all reasonable and the AIDS incidence curves are all similar. Hence the simulations are not very sensitive to changes in the mean incubation period.

Recall that the relative weights of transmission in the four phases are the products of the relative infectivities and the relative sexual activities (as compared to asymptomatic men) of the men in each of the phases. The baseline parameter set values assumed that asymptomatic men were less infectious than men in the other phases and that men with symptoms or AIDS were less sexually active. Changing the baseline relative weights of (2,1,1.5,7.5) in the four phases to (1,1,1,1) causes minor changes in the best–fitting simulation curves. Changing the baseline

relative weights of (2,1,1.5,7.5) to (2,1,0,0), (2,0,1.5,7,5), (10,1,1,1) and (1,1,1,1) causes some small changes in the best–fitting simulation curves, but they all give acceptable fits and the parameter values which give these best fits are consistent with the *a priori* estimates. Thus it is not possible to exclude various possible relative weights of transmission from the fits obtained.

6.4.4 Sexual Behavior Parameters

Satisfying the fit criteria by using the simulation model is not possible if there is no reduction in partnership formation rates. If the simulation with no reductions fits the early AIDS incidence, then the AIDS incidence is too high in later years. This result is consistent with all of the SF surveys described in Chapter 3, which report some decreases in high–risk behavior during part of the time interval from 1982 to 1989.

The simulation results are relatively insensitive to changes in the starting date STR and stopping date STP for the reduction in the average partnership formation rate per month. Changes of these dates by 3 months in either direction lead to best–fitting simulation curves which are very similar to the baseline curves. Changes by 6 months lead to minor changes from the baseline curves.

Ten percent changes in the yearly reduction factor lead to relatively small changes in the simulation curves. When the baseline RDN value of 0.61 is changed to 0.56 or 0.66 and the other parameters are varied to give the best fit, the resulting simulation curves are similar to those for the baseline parameter set. When the average number PAS of new partners per month before reduction is changed by 10%, there are some changes in the best–fitting HIV incidence simulation curves, but the AIDS incidence curves are all close together. For example, when the baseline value of 0.75 for PAS is changed to 0.82, the HIV epidemic curve rises more steeply and falls more steeply; when PAS is changed to 0.67, the best–fitting simulation has a lower and wider HIV incidence curve. Although both simulations give adequate fits to the data curves, the simulations are somewhat sensitive to 10% changes in PAS.

6.5 Conclusions

The AIDS incidence in Table 5.1 increases steadily from 1980 to 1987 and then remains approximately level on a plateau from 1987 to 1989 before increasing again in 1990. As shown in Figure 1.5, this plateau in AIDS incidence in homosexual men also occurred in other cities such as New York City and Los Angeles (CDC, 1989b; Berkelman et al., 1989). An increase in AIDS incidence in homosexual men from 1989 to 1990 also occurred in the entire United States (CDC, 1991a). Thus these trends in AIDS cases in homosexual men are not unique to SF.

Various explanations for the plateau in 1987 – 89 of AIDS cases in homosexual men have been presented (Gail et al., 1990; CDC: 1990a). These include the effects of therapy, behavior change (and possibly saturation) resulting in decreased HIV incidence in the early 1980s, changes in reporting delays or practices, the 1987 change in the AIDS surveillance definition and evolution of attenuated HIV strains. Linden et al. (1989) found that the plateau could not be explained by

late reporting or underreporting. It cannot be due to the 1987 definition change since adjustments for this are made in Table 5.1.

This temporary plateau in the yearly AIDS cases in homosexual men in SF makes forecasting very difficult. The simulations here which fit the data seem to smooth out AIDS incidences from 1987 to 1990. The best–fitting simulations are reasonably consistent since the AIDS incidences usually have a peak in about 1989 and then decrease slowly. This shape is a consequence of the estimated shape of the HIV incidence curve, which has a peak in early 1981 and then declines rapidly until it levels off in 1986 at 720 new infections per year. Thus the peak in the AIDS incidence curve in 1989 is due to the peak in the estimated HIV incidence curve in 1981. If the estimated HIV incidence curve is inaccurate, then the corresponding AIDS incidence curve would also be inaccurate. Our forecasts are based on fits to estimated HIV and AIDS curves; they do not reflect possible changes in sexual behavior after about 1987. Even in SF where good information is available, the fitting of the simulation model is not easy and the remaining uncertainty in the parameter values implies that forecasts from the simulations are also uncertain. Caution should be observed in using simulation modeling for forecasting in other risk groups and regions.

Other forecasts of AIDS incidences in homosexual men in SF have been given. Bacchetti and Moss (1989) gave a range of projections with peak AIDS incidences between 1989 and 1991. Ahlgren et al. (1990) found similar peaks in AIDS incidences using simulation modeling. Thus two other modeling groups have made forecasts similar to ours. Lemp et al. (1990) projected increasing total AIDS incidences (all risk groups) in SF through 1993.

A basic principle which has emerged from the simulations is that the AIDS incidence at a given time is primarily due to the HIV incidence about 6 to 10 years earlier and is less influenced by HIV incidence in the past 5 years and beyond 11 years earlier. This finding is consistent with the distribution curves for the AIDS incubation period in Chapter 2 in which less than 10% develop AIDS in the first five years after infection for $m = 7$. If the estimated HIV incidence were increased by 50% to 1080 per year from 1985 to 1989, then the best–fitting simulation still has a peak AIDS incidence in 1989, but the AIDS incidence decreases more slowly after 1989. Increases or decreases in recent years or in the future in high–risk sexual behavior of homosexual men in SF would affect future AIDS cases.

A group is said to be saturated by an infectious disease if the prevalence of infection is high enough so that transmission decreases significantly due to an insufficient density of susceptibles. A key question is whether the apparent decrease in HIV incidence around 1982 and the plateau in AIDS incidence in 1987 through 1989 in SF homosexual men are exclusively due to saturation in a high–risk group, to changes in sexual behavior, or to both. The results in Section 6.4.4 suggest that there must have been reductions in high–risk behavior, since, otherwise, the fit criteria cannot be satisfied. Because the fit criteria are not satisfied without separate activity level groups, the model must have a very active (high–risk) group. The prevalence in this group reaches 90%, so that there is saturation, with rapid and early spread of HIV infection in the very active (high–risk) group, followed by slower, later spread in the active (lower–risk) group (Table 6.2). Thus both saturation in a high–risk group and changes in sexual behavior are important in

obtaining simulations which satisfy the fit criteria. Since the fit criteria are least satisfied when there are no changes in behavior, behavior modification is more important than saturation.

Fitting a simulation model to data on HIV and AIDS incidence can yield rough estimates of parameter values. For example, the starting dates of the epidemic in the simulations is consistently somewhere in 1975–1976 so it is plausible that the actual HIV epidemic started in SF in this time interval. The starting dates for reduction in the average number of partners per month are usually in 1981 or early 1982; these simulation estimates are consistent with estimates from sexual behavior surveys in SF. The yearly reduction in the average number of sexual partners of 0.61 in the baseline simulation is consistent with the estimates of 0.59, 0.67, 0.43, and 0.70 found from sexual behavior surveys. These and other consistencies between the simulation and *a priori* estimates increase our confidence in these parameter values.

The theoretical implications of a mixture of proportional mixing and internal mixing within each activity level for the development of an AIDS epidemic in populations with different activity levels have been analyzed by using simulations (Jacquez et al., 1988; Blythe and Anderson, 1988; Castillo–Chavez et al., 1989; Kaplan and Lee, 1990). If the sexual–activity–level groups have their sexual contacts distributed by proportional mixing, then the speed of development of the epidemic is similar to the speed for homogeneously mixing populations. However, if the mixing is very biased so that nearly all partners are within the same sexual–activity–level groups, then the overall speed of development is slower, since the disease seems to sweep through the highest sexual–activity–level group, then the second highest sexual–activity–level group, etc. For very weakly connected sexual–activity–level groups, the overall development of the epidemic is similar to the development when the groups are completely disconnected and each group starts with a few infected individuals. The baseline parameter set in Table 6.1 has the external (proportional) mixing fraction η equal to 0.82, but in Section 6.4.2 it has been found that the best–fitting simulations with $\eta = 1$ are almost as good. Thus for modeling the homosexual men in SF, the sexual–activity–level groups are strongly connected so that the simple proportional mixing assumption is adequate.

In Chapter 5 the *a priori* estimates are $\mathrm{PAS} = 2$ for the average number of different sexual partners per month of homosexual men in SF before 1982 and $\mathrm{QH} = 0.05$ for the probability of transmission to a partner by an infected asymptomatic man, so that the average number of partnerships per month of susceptibles which result in transmission is $\mathrm{PAS} \times \mathrm{QH} = 0.1$. The values for the baseline parameter set in Table 6.1 are $\mathrm{PAS} = 0.75$ and $\mathrm{QH} = 0.05$, so that their product is 0.0375, which is less than the *a priori* estimate by a factor of 2.7. This suggests that one or both of the *a priori* estimates were too high; for example, if the *a priori* estimate of $\mathrm{PAS} = 2$ were correct, then a better estimate of QH would be 0.017. In Section 6.4.4 it has been found that the best–fitting simulation curves are sensitive to 10% changes in PAS, so they would also be sensitive to similar small changes in QH. Better estimates of these two parameters would be desirable, but it may be unrealistic to expect to obtain accurate estimates of these parameters from sexual behavior surveys.

In the sensitivity analysis in Section 6.4, the best–fitting HIV and AIDS incidence curves are sensitive to changes in values of some parameters. In Section 6.4.1, they have been found to be sensitive to changes in the yearly migration rate δ. The immigration and emigration rate estimate of 5% per year has been based on one sexual behavior survey (see Chapter 5). If the turnover rate is only 5% per year in the simulations, then the AIDS incidence in former SF residents is 53% of the AIDS incidence in current SF residents. Since this migration parameter is important in forecasting the long–range HIV and AIDS incidence in a risk group, it would be advantageous if questions to determine inflow and outflow rates in risk groups were included in future surveys. Although the simulations are sensitive to the yearly migration rate constant δ, they are not sensitive to the natural mortality rate constant μ or the monthly activity level change rate constants ϕ and θ so that the current estimates of those last three parameters are probably adequate.

The simulation model for the staged progression to AIDS has the advantage that it is consistent with the slow deterioration of the immune system and the decline in CD4 cells. In all of the simulations, the AIDS incidence peak occurs about 8 to 10 years after the HIV incidence peak. This observation is consistent with the median incubation period of 9.6 years for $m = 7$. When the progression to AIDS is slower or faster, the delay from the peak in HIV incidence to the peak in AIDS incidence is longer or shorter, as seen in Figure 6.4, but the overall patterns in the HIV and AIDS incidences are the same.

Although there is a large amount of information on HIV and AIDS in homosexual men in SF, the values of some parameters are still uncertain and the sensitivity analyses show that these uncertainties lead to variabilities in the fits to the estimated HIV and AIDS incidences. For example, very little information is available on the relative infectivity or the relative partnership formation rates of HIV–positive men in the stages leading to AIDS. The sensitivities to the relative weights of transmission, which are the products of the corresponding relative infectivities and relative sexual activities, are analyzed in Section 6.4.3. The fits are almost as good when the relative weights of transmission are (10,1,1,1) for the four phases as when the weights are (2,1,1.5,7.5); this agrees with the suggestion of Ahlgren et al. (1990) that the HIV incidence could be due to a high infectivity of infected people in the short pre–antibody phase. Adequate fits are also obtained when the relative weights of transmission are (1,1,1,1) or (2,1,0,0) or (2,0,1.5,7.5) so that it is not possible on the basis of the fit to the data to exclude any possibilities regarding the relative infectivity and sexual activity of individuals in the various stages

Therapy with zidovudine delays the onset of AIDS and increases AIDS survival times, at least in some patients. In Section 6.3 the simulation model is modified to incorporate treatment of AIDS and final–stage symptomatic patients. Simulations using the estimated percentages treated (Lang et al., 1991) give marginally adequate fits to the data. Simulations with half as many treated and with no treatment give better fits. These simulations suggest that the percentages treated effectively with zidovudine may be lower than originally estimated by Lang et al. (1991). It is clear that more and better data are needed on the effects of therapy.

The dynamic simulation model formulated in Chapter 3 is designed to incorporate all features considered essential for modeling the sexual spread of HIV infections in homosexual men

in SF and yet is also designed to be simple enough so that estimating the values of the parameters is possible. Most of the parameter values have been estimated from various data sources and the remaining few parameters have been adjusted to fit the estimates of HIV and AIDS incidence for homosexual men in SF. Thus the simulation modeling provides a conceptual and quantitative means of organizing, coalescing and cross–checking diverse information on homosexual men in SF. The simulation modeling has evaluated the relative roles of saturation and behavior modification, shown that there must be a high–risk very sexually active group, shown that the sexual–activity–level groups are strongly connected, estimated parameter values, and identified the most sensitive parameter values so that data can be collected to get improved estimates.