CHAPTER 2

MODELING THE PROGRESSION OF HIV–INFECTED PERSONS TO AIDS

Since people who are infected with HIV seem to progress through various stages or phases towards AIDS and death due to AIDS (Redfield et al., 1986; Seligman et al., 1987), a natural model for this progression is through a sequence of five phases (Hethcote, 1987, 1989; Longini et al., 1989, 1990). The first phase is the pre–antibody period, in which a person is infected, but not antibody seropositive. Some people in this first phase have acute illness. The second phase includes persons who are infected and antibody seropositive, but are asymptomatic. The third phase (symptomatic) occurs when the person develops an abnormal hematologic indicator and/or prodromal illnesses such as persistent generalized lymphadenopathy or oral candidiasis. The fourth phase is clinical AIDS, and the fifth phase is death due to AIDS. In Section 2.1 the asymptomatic and symptomatic phases are subdivided into stages in order to provide enough flexibility to match the HIV prevalence and AIDS incidence data in SF. If the number m of infectious stages is even, then the numbers of asymptomatic and symptomatic stages are equal to $(m-2)/2$; otherwise, they are $(m-3)/2$ and $(m-1)/2$, respectively.

As information about the effects of HIV on the immune system has accumulated, it has become clear that the progress towards AIDS coincides with a decline in the number of $CD4^+$ T–lymphocytes (T4 cells). Thus T4 cell count intervals can be used as stages and the progression through these stages can be measured. Longini et al. (1991) have used a continuous–time Markov process to model the decline of T4 cells in HIV–infected persons. The stages and mean waiting times are given in Section 2.2. This second staged progression model is probably more precise since it is based on quantitative laboratory measurements instead of the clinical symptoms involved in the first progression model.

The progression of HIV–infected children to AIDS is significantly different from that of adults (Auger et al., 1988). Some children progress rapidly, while others progress more slowly. In Section 2.3 a staged progression model for children with fast and slow tracks is formulated and parameter values are estimated. This model for the progression of children is used in later chapters for the children of female intravenous drug users (IVDUs) and female heterosexual partners of male IVDUs.

2.1 Staged Progression Based on Clinical Phases

The AIDS incubation period is the time from HIV infection until the development of AIDS. A variety of distributions such as the Weibull, gamma and normal have been used to fit AIDS incubation period data (Lui et al.,1988; Medley et al., 1987; Rees, 1987); however, a staged progression model is more useful for simulations. The model here results in a generalized gamma distribution for the AIDS incubation period (Longini et al., 1989,1990).

This staged progression model has five phases: pre–antibody, asymptomatic, symptomatic, AIDS and death. Longini et al. (1989) estimated the transition rate constants between these phases from censored data on 603 individuals who have HIV infections by using a

Table 2.1. Transition rate constants and mean waiting times in clinical phases.

Clinical phase	estimates ± std. error in months^{-1}	mean waiting time in months(years)	median waiting time in months (years)
pre–antibody	0.4571±0.1381	2.2 (0.2)	1.5 (0.1)
asymptomatic	0.0190±0.0022	52.6 (4.4)	36.5 (3.0)
symptomatic	0.0159±0.0018	62.9 (5.2)	43.6 (3.6)
AIDS	0.0424±0.0044	23.6 (2.0)	16.3 (1.4)

five–phase, time–homogeneous, Markov model with a negative exponential waiting time in each phase. Their estimates (Table 2.1) yield a mean incubation period from HIV infection to AIDS of 9.8 years (117.7 months), with a 95% confidence interval of [8.4; 11.2] years.

Payne et al. (1989) reported a median survival time of 12.5 months for 4524 AIDS patients in SF between July 1981 and December 1987. Survival time is the time from diagnosis of AIDS to death. Lemp et al. (1990) reported a median survival time of 12.1 months for patients in the SF Vaccine Trial Cohort; but this was 14.4 months for patients diagnosed in 1986 and 1987 (presumably due to therapy or better care). Thus the median survival time of AIDS patients (without therapy) seems to be approximately one year. The median survival time of 16.3 months in Table 2.1 may be longer because some of the AIDS patients were lost to follow–up, and their deaths were not recorded. Consequently, a 12.5 month median survival time is used; this corresponds to a mean survival time of 18.0 months, and a transition rate constant equal to 0.0555. This transition rate constant has no effect on AIDS incidence, but it does affect the AIDS prevalence and the AIDS death rate. The incidence of a condition such as HIV infection or developing AIDS is the number of persons contracting the condition per unit time, which is not the same as the prevalence, which is the number of people with the condition at the given time.

The asymptomatic and symptomatic phases are subdivided into stages so that the cumulative distribution function for the AIDS incubation period matches the data. For example, if $m = 7$, the transition rate constants are $\gamma_1 = 0.4571$ for the pre–antibody stage, $\gamma_2 = \gamma_3 = 2 \times 0.0190$ for the two asymptomatic stages, $\gamma_4 = \gamma_5 = \gamma_6 = 3 \times 0.0159$ for the three symptomatic stages and $\gamma_7 = 0.0555$ for the AIDS stage. The staged progression model for $m = 7$ is shown in Figure 2.1.

Figure 2.2 shows the graphs for 5, 6, and 7 stages of the fraction who have developed AIDS as a function of time since HIV infection, i.e., the cumulative distribution functions. Figure 2.2 also shows data on fractions progressing to AIDS from three additional sources with smaller data sets than used in Longini et al. (1989). Lifson et al. (1990) used data on 268 men in the San Francisco City Clinic Cohort (SFCCC) to estimate the fraction who developed AIDS each year after infection; their median AIDS incubation period is between 9 and 10 years. From an analysis of the hepatitis B vaccine trial cohort in the SFCCC, Bacchetti and Moss (1989) found that 20.8% developed AIDS within the first 6 years and 51.2% within 10 years; their median

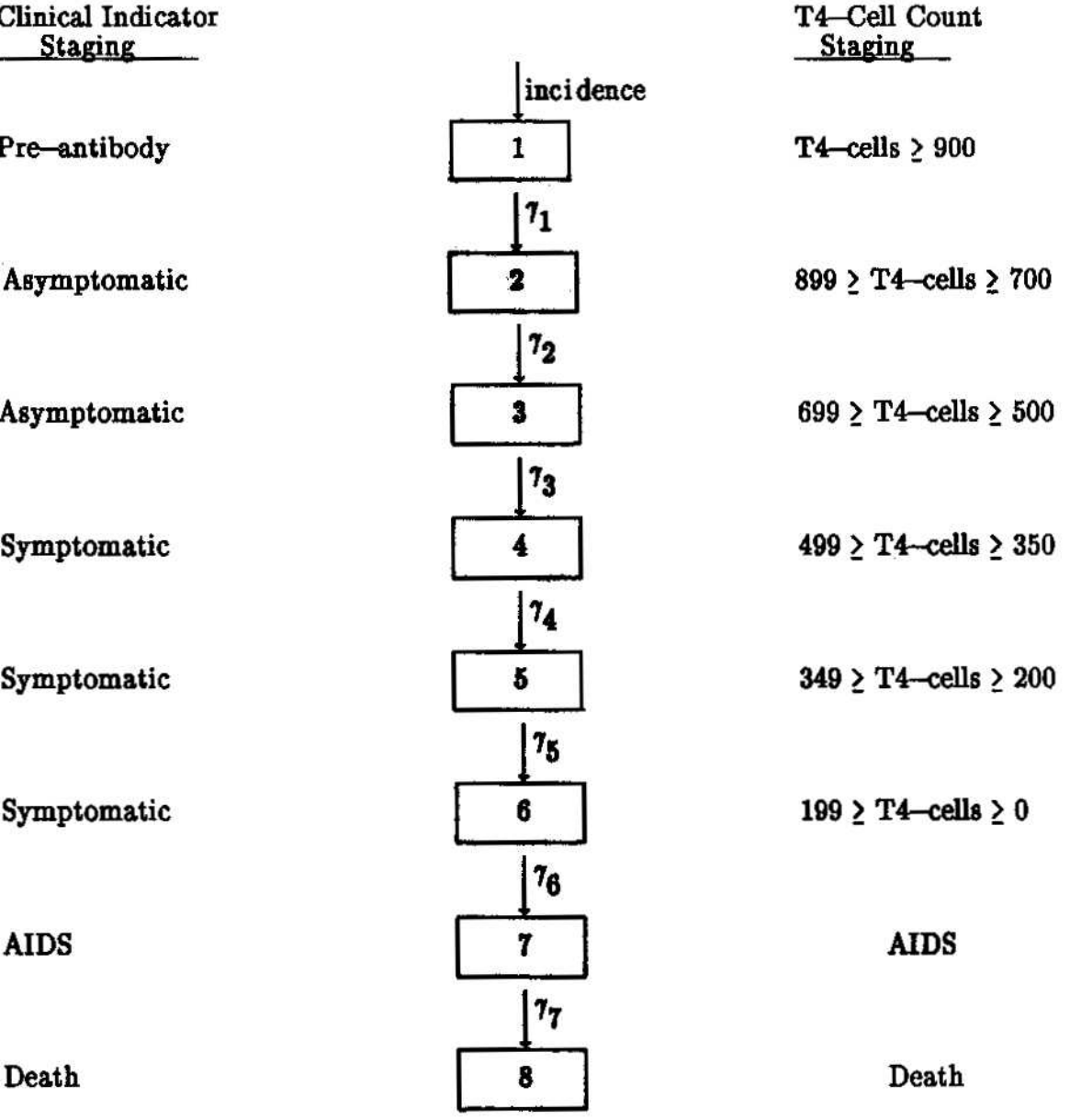

Figure 2.1. The staged model based on clinical indicators or T4–cell counts for progression to AIDS and death when there are 7 infectious stages (6 stages before AIDS).

AIDS incubation period is 9.8 years. Hessol et al. (1989) used data on 135 hepatitis B vaccine trial participants to get a Kaplan–Meier survival curve of the cumulative proportions of men with AIDS by duration of HIV infection.

The cumulative distributions of Lifson et al. (1990) and Bacchetti and Moss (1989) agree with each other in Figure 2.2, but the Hessol et al. (1989) distribution does not. Their cumulative distribution curves are roughly consistent with the $m = 5, 6, 7$ curves based on the data in Longini et al. (1989), except that their curves are lower at 10 and 11 years. Their estimates are probably low at longer times because therapy with zidovudine and pentamidine has delayed the onset of AIDS for many treated patients in their cohorts.

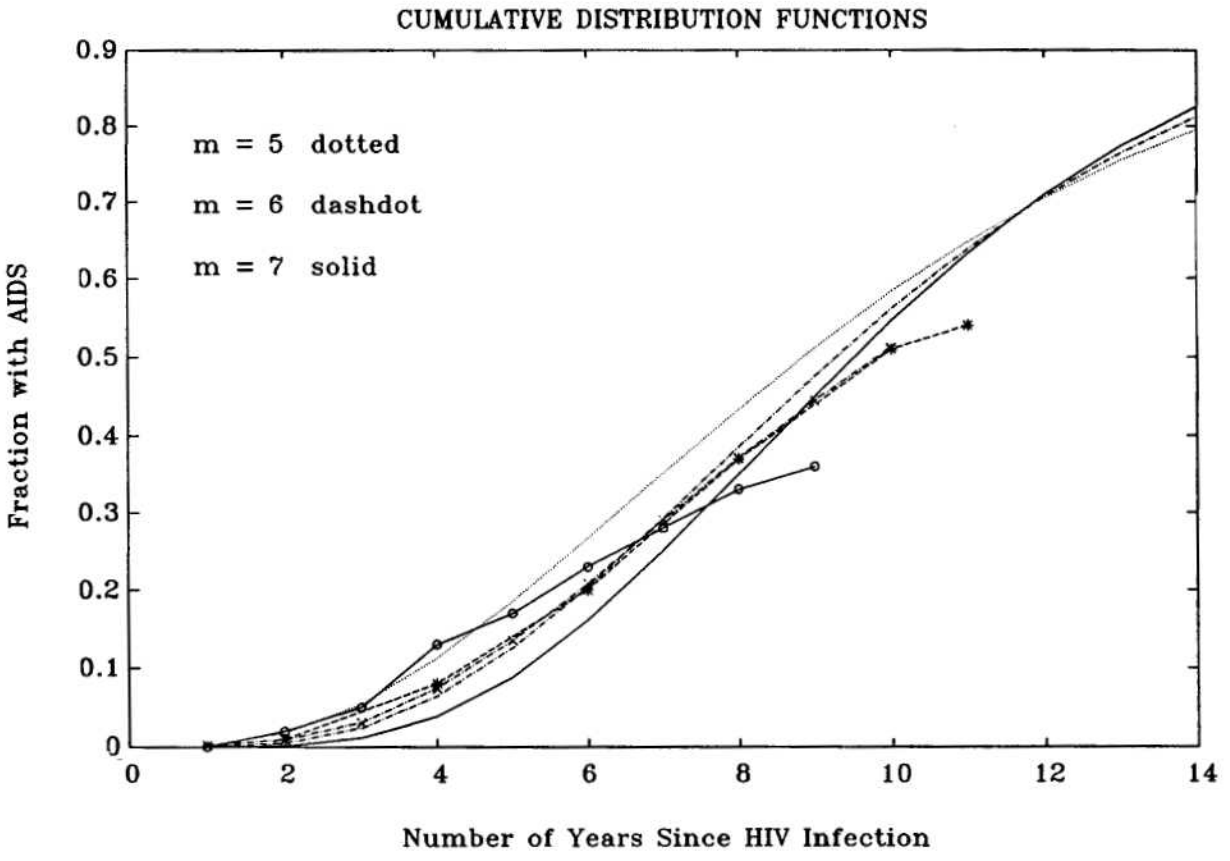

Figure 2.2. Cumulative distribution functions for developing AIDS based on data of Longini et al. (1989), where the number of infectious stages is $m = 5$, 6, or 7. The symbol o is used for the data of Hessol et al. (1990), * for that of Lifson et al. (1990), and x for that of Bacchetti and Moss (1989).

2.2 Staged Progression Based on T4 Cell Counts

The CD4$^+$ T–lymphocytes (T4 cells) are a primary target of HIV in the host, and the decline in T4 cells is an important indicator of progression towards AIDS. Thus it is logical to use T4 cell decline in a staged progression model. Longini et al. (1991) defined six stages of HIV infection for individuals who have not yet been diagnosed with AIDS (technically, who have developed an opportunistic infection corresponding to the Walter Reed stage six (Redfield et al., 1986). These six stages correspond to T4 cell count intervals given in Table 2.2. The transition rates between these stages were estimated from data on 1796 HIV–positive individuals in the United States Army using a continuous–time Markov process model. The transition rate constants and mean waiting times are given in Table 2.2.

Since T4–cell levels in individuals can vary due to measurement error and changing physiological conditions, Longini et al. (1991) use a persistance criteria that two consecutive measurements are needed to confirm a true reduction in T4–cell count. The estimated mean waiting time from seroconversion to when the T4 cell count is persistently below 500 is 4.1 years, the mean waiting time until it is below 200 is 8.0 years, and the mean waiting time from seroconversion to AIDS diagnosis (technically, diagnosis with Walter Reed stage 6 opportunistic infection) is 9.6 years. The data were also analyzed for three age groups ($\leq$ 25, 26–30, and

Table 2.2 Estimated parameters, γ, and mean waiting times, μ, in each stage of infection with no cofactors. Standard errors are in parentheses.

Stage i	T4–cell count interval	Transition rate $\hat{\gamma}_i$ in months^{-1}	Mean waiting time $\hat{\mu}_i$ in years	Cum. waiting time in years
1	> 899	0.0764 (0.0051)	1.1 (0.1)	1.1 (0.1)
2	700 – 899	0.0665 (0.0033)	1.3 (0.1)	2.4 (0.1)
3	500 – 699	0.0499 (0.0021)	1.7 (0.1)	4.1 (0.1)
4	350 – 499	0.0429 (0.0019)	1.9 (0.1)	6.0 (0.1)
5	200 – 349	0.0408 (0.0022)	2.0 (0.1)	8.0 (0.2)
6	1 – 199	0.0529 (0.0035)	1.6 (0.1)	9.6 (0.2)

> 30), and although the progression rates were the same for T4 cell counts $\geq$ 500, the two older groups progressed faster when T4 cell counts were < 500. Although age is a cofactor, it is not considered in our model.

It seems likely that T4 cell counts will become the most widely used marker for HIV progression. They are currently used as indicators for starting zidovudine, other antiviral treatments and PCP prophylaxis with aerosol pentamidine. The T4 cell counts will probably also be used as surrogate endpoints in clinical trials of therapies and vaccines. Under certain conditions, the use of surrogate endpoints can significantly shorten the clinical trials needed for testing and approval of drugs and vaccines (Machado et al., 1990).

2.3 Staged Progression for Children

Auger et al. (1988) give the AIDS incubation cumulative distribution function for 215 pediatric AIDS patients. The mean incubation period is shorter for these children and there is an initial steep rise followed by a slower increase. They found that approximately 20% develop AIDS in the first year of life and the remainder develop AIDS at a nearly constant rate of 8% per year. Thus a reasonable model might have a subgroup of fast progressers and a second subgroup of slower progressers.

The progression model for adults is modified as shown in Figure 2.3 so that a fraction p of pediatric HIV infecteds progress rapidly through one stage with a negative exponential waiting time and a removal (to AIDS) rate constant b. The fraction $1-p$ move through six stages with rate constants in each stage given by $a\gamma_i$ where γ_i is the rate constant for the corresponding adult stage given in Table 2.2. Thus the mean incubation period for those who progress rapidly is 1/b and the mean incubation period for those who progress more slowly is (9.8/a) years.

The best fit to the data of Auger et al. (1988) has parameter values of $p = 0.34$, $b = 0.08$, $m = 7$, and $a = 1.55$ so the mean incubation periods are 12.5 months and 6.3 years for those who progress rapidly and slowly, respectively. Note that about one–third of the children progress

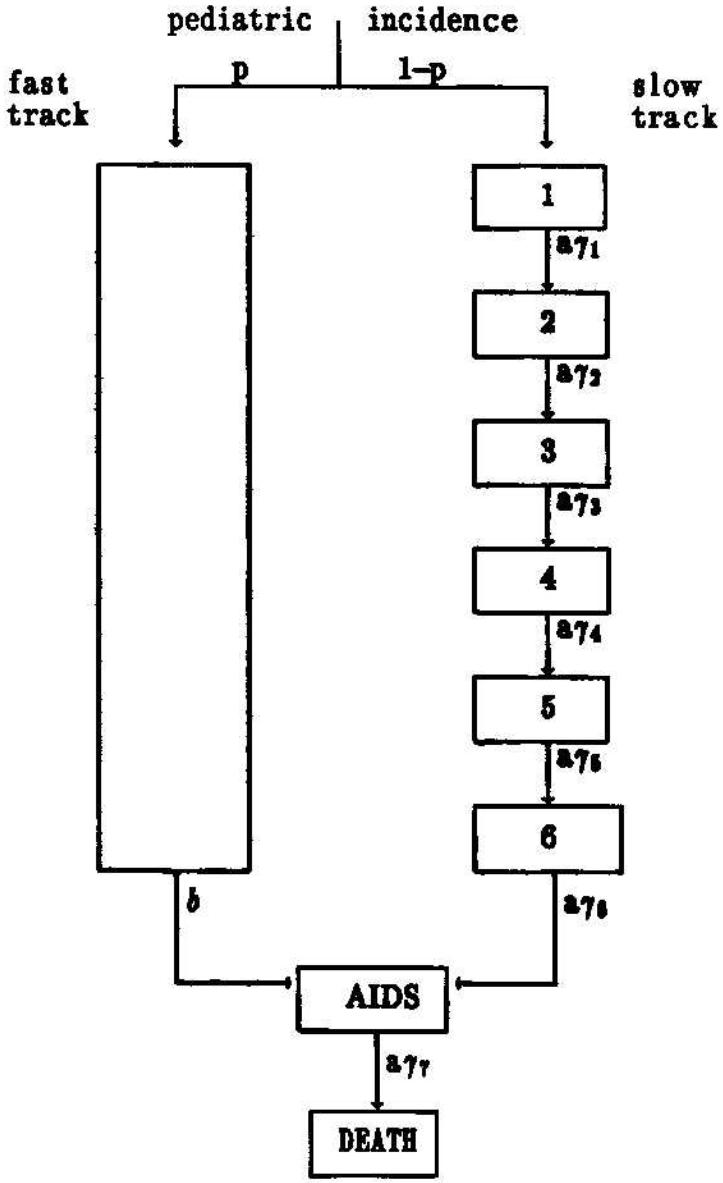

Figure 2.3. Progression of children to AIDS and death showing slow and fast tracks.

rapidly and two–thirds progress slowly. The data points and cumulative distribution function for the parameters above are shown in Figure 2.4.

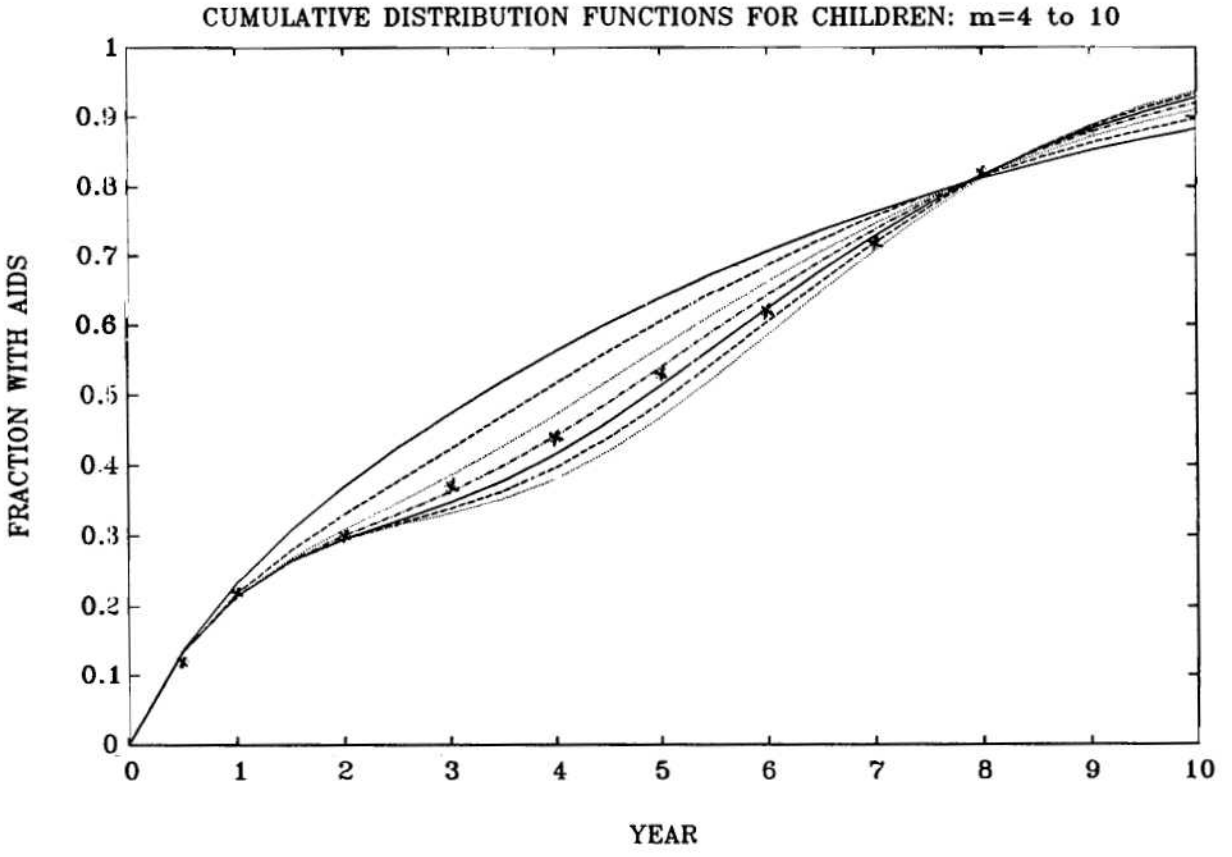

Figure 2.4. Cumulative distribution functions for developing AIDS in pediatric HIV–infected patients with parameters $a = 1.55$, $p = 0.34$, $b = 0.08$, and $m = 4$ (top) to 10 (bottom). The $m = 7$ curve matches the data points * of Auger et al. (1988).