

Impact of ART on Survival

Data on the effect of antiretroviral therapy (ART) on survival are not prolific, and those data that exist are not necessarily directly relevant to the current Thai experience with ART. To model the effect of ART on the dynamics of the Thai epidemic, we must infer from the existing studies a detailed quantitative profile of survival and progression, one that captures not only deaths but also treatment failure and dropout behavior. We first describe our assumptions regarding the rate of progression of patients in the absence of ART. We then show the progression patterns that we have inferred for patients on ART under various assumptions regarding their CD4 count on entry and the degree of support they receive for adherence. We also must assume how patients who make the transition to second-line therapy would progress. Finally, we discuss our assumptions regarding the effect of early recruitment on survival.

Progression without ART

A seminal study by Rangsin and others (2004) presents survival data over seven years on two samples of Thai men, of whom 235 are HIV positive and 255 are HIV negative. The HIV-positive men are followed from the date of HIV infection up to a maximum of seven years. The HIV-negative men are followed for an equal length of time. The mortality rate among the HIV-negative men was 3.1 percent; among the HIV-positive men it was 32.8 percent—ten times higher.

Table A.1 presents the annual survival data from Rangsin and others (2004) and replicates in columns (7) through (9) the survival statistics they calculate.¹ Figure A.1 shows the graph of the column (9) survival statistics against time. The figure, which is referred to in epidemiology as a *Kaplan-Meier survival curve*, shows the percentage of the initial cohort who remain alive at each date in the future. Note that the curve begins with 100 percent of the cohort at time zero and descends to 65 percent of the cohort after seven years. If the time of death or loss to follow-up were known very precisely for each patient, no two patients would be likely to drop out at exactly the same time, so the curve would be smooth. In most real-life studies, the time of death or dropout is only known within an interval. Therefore, several subjects are often lost during a single interval of time. In the figure this lack of precision in the data is represented by the flat spots in the survival curve. The width of each flat spot represents a period of time over which the subjects are observed. The vertical drop from one “step” down to the next represents the number of subjects who died at that point. Subjects who are followed for part of the study period and then drop out contribute to the statistics on survival until they drop out, but they are excluded from the analysis after that point. If their fate is unknown, they cannot be considered to have either survived or died, so they are simply omitted from the denominator as soon as they are lost to follow-up.

In addition to the survival curve, figure A.1 also presents the statistical 95 percent confidence interval for that curve. The interval is a measure of the accuracy with which one can estimate the survival patterns in the 1990s of the population of all HIV-infected Thai men from this sample of 235 men, assuming that the sample was drawn at random. The interval is fairly narrow at the beginning of the period but becomes wider as the sample size decreases over time.

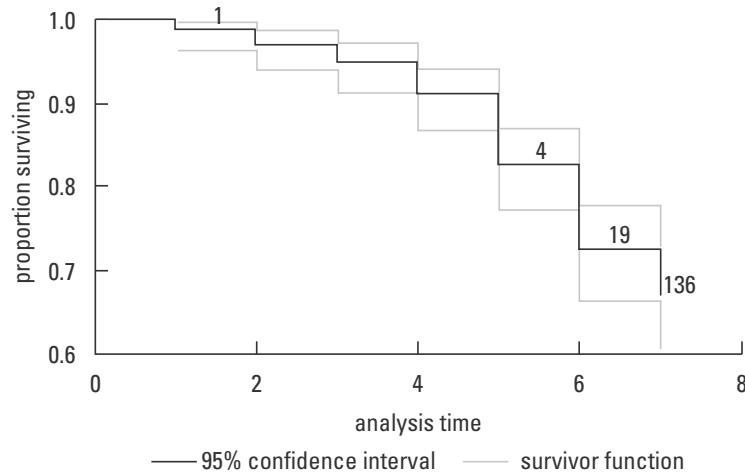
For the purpose of the projection model, we need to project survival far beyond the 7-year time horizon of these data out to more than 20 years after infection. The difficulty of doing this task with precision is suggested by the fact that the confidence interval in figure A.1 widens to more than 10 percentage points by year 7. Furthermore, the data in that figure were collected at a time when Thai men had less access to good treatment for opportunistic infections than has more recently been the case. Therefore, to construct a plausible survival pattern for Thai people without AIDS in the current decade, we

Table A.1 Survival of 235 Thai HIV-Positive Men

<i>Years HIV+</i> (1)	<i>Alive at start of year</i> (2)	<i>Lost to follow-up</i> (3)	<i>Actuarial adjusted at risk</i> (4)	<i>Deaths</i> (5)	<i>Alive at end of year</i> (6)	<i>One-year hazard (%)</i> (7)	<i>Adjusted one-year hazard (%)</i> (8)	<i>Adjusted Kaplan-Meier survival (%)</i> (9)
1	235	1	234.5	3	231	1.3	1.3	98.7
2	231	0	231	4	227	1.7	1.7	97.0
3	227	0	227	5	222	2.2	2.2	94.9
4	222	0	222	9	213	4.1	4.1	91.0
5	213	4	211	20	189	9.4	9.5	82.4
6	189	19	179.5	23	147	12.2	12.8	71.8
7	147	80	107	11	56	7.5	10.3	64.5
Totals		104		75				

Source: Rangsin and others 2004.

Note: Columns (1), (5) and (6) reproduce the first and the two last columns of table 2 in Rangsin. Columns (2), (3) and (4) are interpolated in order to be consistent with the published data in Rangsin's table 2. Column (7) is calculated simply as column (5) divided by column (2). Column (8) makes the so-called actuarial adjustment used by life-tables and by Rangsin. Column (9) applies the standard formula for the Kaplan-Meier product limit survival rate to column (8) and succeeds in replicating the Rangsin calculations.

Figure A.1 Survival Curve for a Cohort of 235 HIV-Positive Thai Men

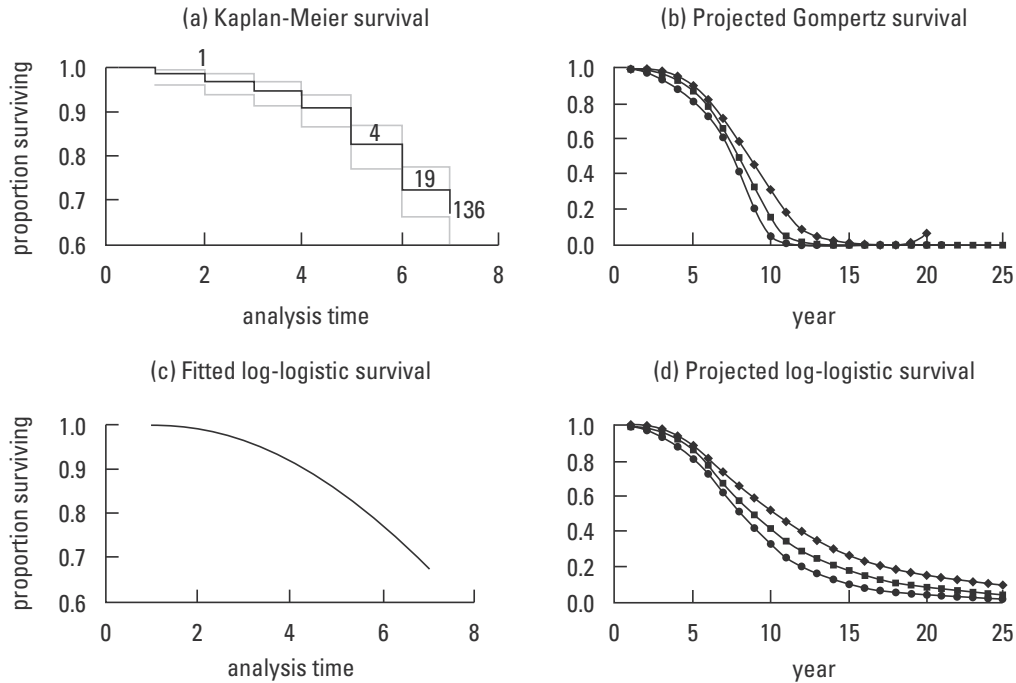
Source: Rangsin 2004, table 2.

Note: This figure is not identical to Rangsin's survival curve, because it uses the grouped data rather than the original data.

need to adjust a curve based on the Rangsin data to more closely approximate the better survival patterns experienced without ART in other parts of the world. We return to this point in a few paragraphs. However, first we will examine how to use annual survival data like these in a model that projects 20 or more years into the future.

Making a projection of survival beyond the available data amounts to fitting the data to one of several possible functional forms and then projecting on the basis of a choice among these functional representations. The four panels of figure A.2 show the results of such a projection. The panel (a) replicates for easy reference the survival curve from figure A.1. The panel (c) shows the result of fitting one particular functional form, the log-logistic, to the data. Panel (d) projects that log-logistic function into the future with a 95 percent confidence interval. Panel (b) shows how the projected curve and its confidence interval would change if the functional form were the Gompertz instead of the log-logistic.

Note the extreme sensitivity of the results in outer years to the selection of functional form. The log-logistic function is much more optimistic about projected survival than is the Gompertz. At year 10, the log-logistic projects that 41.1 percent of HIV-infected people would still be alive without ART, whereas the Gompertz projects that only 13.4 percent would be alive. We also fit and projected with the Weibull function, which predicts that an intermediate percentage of 33.5 would be alive in year 10.²

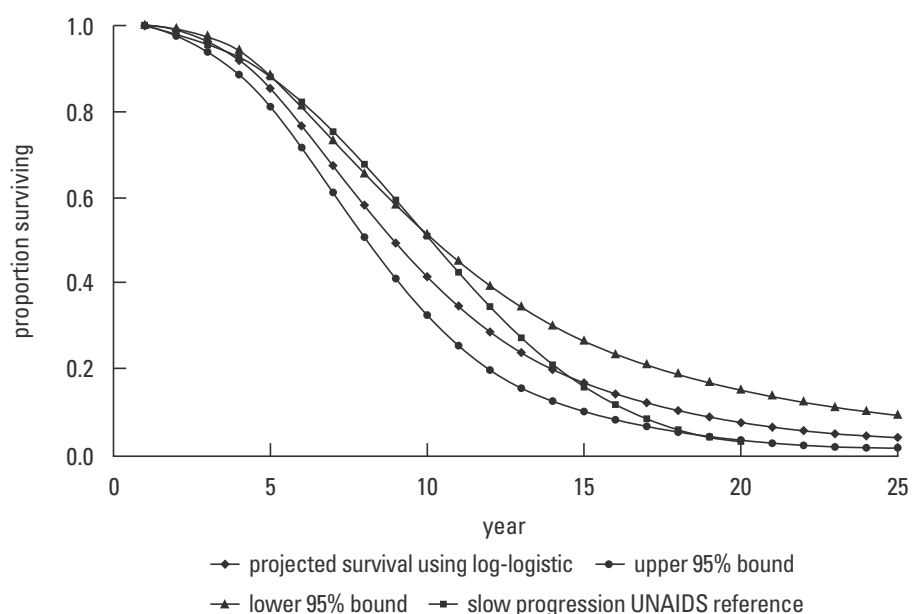
Figure A.2 Projecting Survival without ART

Source: Rangsin and others 2004; authors' calculations.

Initial efforts to recalibrate the 1997 version of the Asian Epidemic Model (AEM) to current data used the progression rate without AIDS given by the above log-logistic function fitted to the Thai data from Rangsin (2004). However, projections using this fast progression rate predict that the total number of symptomatic AIDS patients in 2004 would be fewer than 30,000. Because data from the Thai Ministry of Public Health (MOPH) indicate that as many as 40,000 people are currently receiving ART, almost all of whom were symptomatic when recruited, this projection seems to be substantially too low for the current year. From this finding and from the observation that treatment for opportunistic infections has improved in Thailand since the data analyzed by Rangsin were collected, we conclude that the survival experience of patients without ART has recently been better than could have been predicted five years ago from the Thai data.

As an alternative to relying entirely on a projection from the Rangsin data, we turn to the advice of the Joint United Nations Programme on HIV/AIDS (UNAIDS) Reference Group on Estimates, Modeling, and Projections, as presented in their published report (Ghys and others 2004) and in Stover (2002). Figure A.3 compares the log-logistic projection from the Rangsin data with the slow survival pattern without ART

Figure A.3 Comparison of Survival Curve Estimated from Thai Data with Survival Curve Recommended by UNAIDS Reference Group



Source: Projection and confidence interval are authors' calculations; UNAIDS reference survival rates are the average of the "slow men" and "slow women" rates from Stover's table 2 (2002, 19).

that is suggested by UNAIDS.³ Note that the pattern suggested by UNAIDS is close to the upper bound of the confidence interval of the first 10 years of the projection from the Thai data and then turns much more pessimistic.

The Impact of ART with and without Support from Groups of People Living with HIV/AIDS

The existing data on the impact of ART on the rate of disease progression of AIDS patients are summarized in background papers to this report. Because none of the available studies is as complete as the Rangsin data for patients without access to ART, the authors of the clinical background studies have provided, through a partly subjective process, synthetic progression data for each scenario in our simulation model. Table A.2 presents these synthetic data for hypothetical cohorts of 100 patients beginning ART in each of two situations.

Panel (a) of table A.2 presents those lost to follow-up, those moved to second-line therapy (because of treatment failure), and those who

Table A.2 Synthetic Survival Data on 100 Hypothetical AIDS Patients on First-Line ART in Thailand: Late Recruitment

<i>(a) Scenario D1 first-line ART without strong PHA groups to facilitate adherence</i>									
<i>Years HIV+ (1)</i>	<i>Start of period (2)</i>	<i>Length of period (3)</i>	<i>Lost to follow-up (4)</i>	<i>Move to second-line (5)</i>	<i>Deaths (6)</i>	<i>End of period (7)</i>	<i>Hazard per period (%) (8)</i>	<i>Kaplan-Meier survival rate (%) (9)</i>	
1	100	1	12	3	10	75	10.0	90.0	
2	75	1	8	5	5	57	6.7	84.0	
3	57	1	5	5	3	44	5.3	79.6	
5	44	2	5	8	3	28	6.8	74.2	
10	28	5	3	6	3	16	10.7	66.2	
15	16	5	3	3	3	7	18.8	53.8	
20	7	5	3	1	3	0	42.9	30.7	
Total		20	39	31	30				

<i>(b) Scenario D3 first-line ART with strong PHA groups to facilitate adherence</i>									
<i>Years HIV+ (1)</i>	<i>Start of period (2)</i>	<i>Length of period (3)</i>	<i>Lost to follow-up (4)</i>	<i>Move to second-line (5)</i>	<i>Deaths (6)</i>	<i>End of period (7)</i>	<i>Hazard per year (%) (8)</i>	<i>Kaplan-Meier survival rate (%) (9)</i>	<i>Kaplan-Meier improvement (D3-D1) (%) (10)</i>
1	100	1	10	0	10	80	10.0	90.0	0.0
2	80	1	5	5	3	67	3.8	86.6	2.6
3	67	1	5	5	3	54	4.5	82.7	3.2
5	54	2	5	8	2	39	3.7	79.7	5.5
10	39	5	2	6	2	29	5.1	75.6	9.4
15	29	5	2	3	1	23	3.4	73.0	19.2
20	23	5	1	1	1	20	4.3	69.8	39.1
Total		20	30	28	22				

Source: Gold and others 2005.

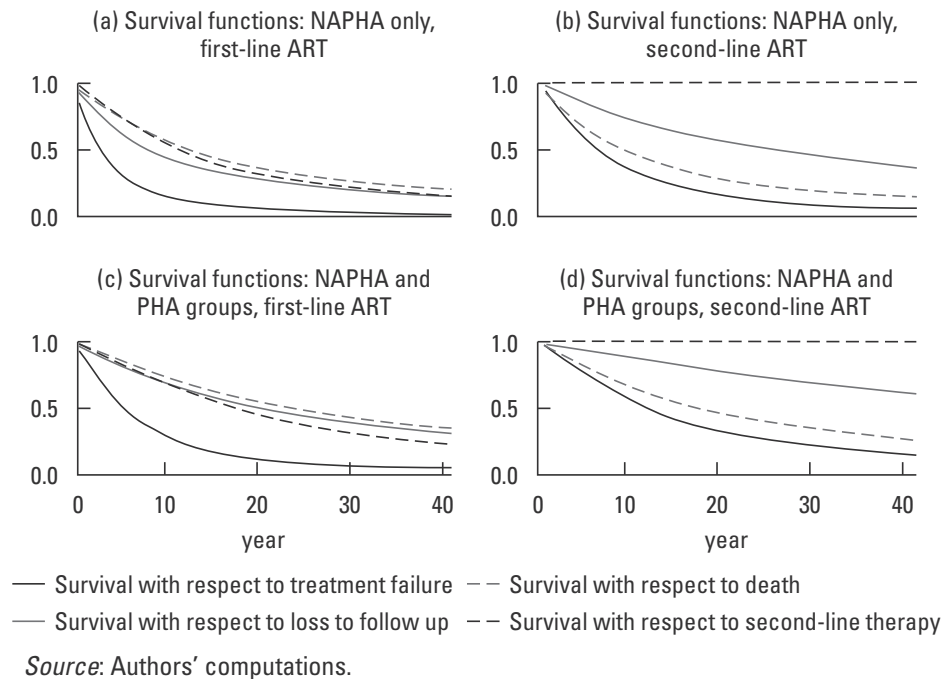
have died when adherence is the individual responsibility of the patient and his or her family, without benefit of a supportive non-governmental organization (NGO). Panel (b) shows the improvement in survival and in retention in first-line therapy when a strong NGO, perhaps staffed with volunteers who themselves are HIV infected, helps patients adhere to medication, show up for appointments to have tests taken, and the like. The last column of the bottom panel gives the number of percentage points in improvement of the survival rate attributable to the supportive NGO or group of people living with AIDS (PHAs). The improvement steadily increases from 5 percentage points at 5 years to 19 points at 15 years and then to 39 points at 20 years.

To capture these progression patterns in a simulation model such as the AEM, in which time is measured in tenths of a year, one must interpolate the survival pattern and then compute the survival density for each category of patient. The problem is complicated by the fact that we must estimate from table A.2 the probability of each of the three events that might cause a person to leave first-line therapy. Rather than omitting from the denominator those lost to follow-up, as is the practice in standard survival analysis, we must estimate the probability that a person will leave first-line therapy for that reason, so that we can model that person's return to the pool of HIV-infected people who are not on ART. (The AEM can then return them to the non-ART progression pattern or reexpose them to ART recruitment.) We also need to estimate the probability of a person moving to second-line therapy, so that in scenarios that include this possibility we can model that flow of patients. We must also estimate the probability of death.

Our approach is to treat departure from first-line therapy for any reason as "failure," grouping together the three possible reasons for such a departure. Using this aggregation of the data, we estimate a survival curve without any data censoring. We then decompose the probability of leaving first-line therapy into its three component parts: loss to follow-up, movement to second-line therapy, and death. The results of the initial estimation and its decomposition into the three components is presented in the panels (a) and (c) of figure A.4.

Using the same Delphi-like approach, the authors of our clinical background paper have estimated the progression pattern of 100

Figure A.4 Progression from First- and Second-Line Therapy with and without PHA Group Support of Adherence Behavior: Late Recruitment



patients who initiate second-line therapy after first-line therapy failed (table A.3).

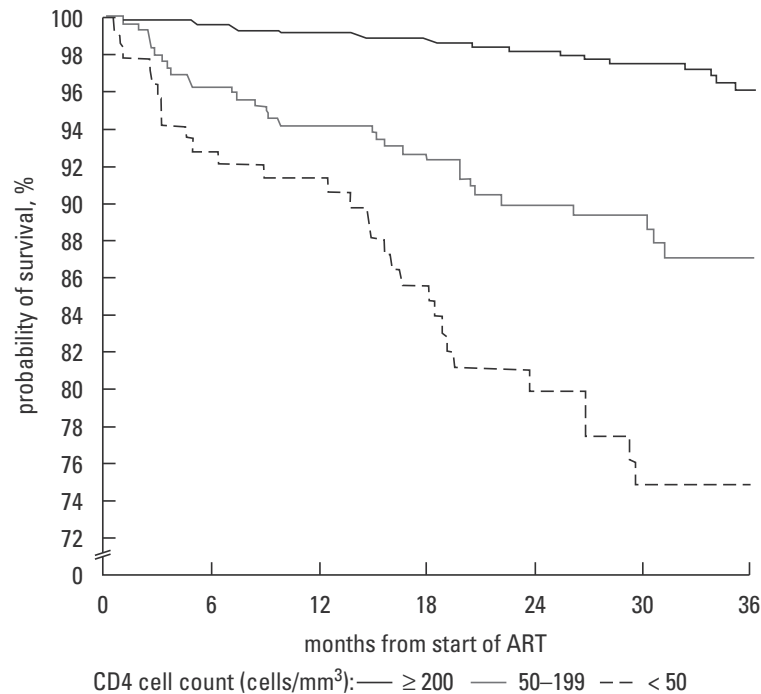
Early versus Late Recruitment

According to the study from Jongkol and others (2004) in Thailand, the median CD4 count for patients entering ART through NAPHA (National Access to Antiretrovirals Program for People Living with AIDS) is 45 cells per cubic millimeter. It is established in the international literature that the success of ART depends critically on the state of the individual's immune system at the time treatment is initiated. See, for example, Hogg and others 2001; Mellors and others (1997). Figure A.5 reproduces the figure from Hogg and others (2001), which shows that the probability of three-year survival drops from 96 percent for those starting treatment at CD4 counts higher than 200 cells per cubic millimeter, to 87 percent for those with counts between 50 and 200 cells per cubic millimeter, down to only 75 percent for those beginning treatment at CD4 counts lower than 50 cells per cubic millimeter.

Table A.3 Synthetic Survival Data on 100 Hypothetical AIDS Patients on Second-Line ART in Thailand: Late Recruitment

<i>(a) Scenario D1 second-line ART without strong PHA groups to facilitate adherence</i>								
<i>Years HIV+ (1)</i>	<i>Start of period (2)</i>	<i>Length of period (3)</i>	<i>Lost to follow-up (4)</i>	<i>Deaths (5)</i>	<i>End of period (6)</i>	<i>Hazard per period (%) (7)</i>	<i>Kaplan-Meier survival rate (%) (8)</i>	
1	100	1	4	8	88	8.0	92.0	
2	88	1	4	8	76	9.1	83.6	
3	76	1	3	10	63	13.2	72.6	
5	63	2	5	10	48	15.9	61.1	
10	48	5	5	11	32	22.9	47.1	
15	32	5	5	11	16	34.4	30.9	
20	16	5	5	11	0	68.8	9.7	
Total		20	31	69				
<i>(b) Scenario D3 second-line ART with strong PHA groups to facilitate adherence</i>								
<i>Years HIV+ (1)</i>	<i>Start of period (2)</i>	<i>Length of period (3)</i>	<i>Lost to follow-up (4)</i>	<i>Deaths (5)</i>	<i>End of period (6)</i>	<i>Hazard per period (%) (7)</i>	<i>Kaplan-Meier survival rate (%) (8)</i>	<i>Kaplan-Meier improvement (D3–D1) (9)</i>
1	100	1	1	6	93	6.0	94.0	2.0
2	93	1	1	6	86	6.5	87.9	4.3
3	86	1	1	6	79	7.0	81.8	9.2
5	79	2	3	8	68	10.1	73.5	12.4
10	68	5	3	8	57	11.8	64.9	17.8
15	57	5	2	8	47	14.0	55.8	24.9
20	47	5	2	8	37	17.0	46.3	36.6
Total			20	13	50			

Source: Gold and others 2005.

Figure A.5 Cumulative Mortality by Baseline CD4 Counts

Source: Hogg and others 2001.

Notes

1. To replicate the authors' calculations, one must apply the so-called actuarial adjustment.

2. The median survival times for the three functional forms were ranked in the same way. The most optimistic function, the log-logistic, yields a median survival of 8.89 years, whereas the Gompertz and the Weibull functions yield 7.89 and 8.50 years, respectively.

3. The slow progression UNAIDS reference pattern in figure A.3 is computed as one minus the average of the male and female cumulative probabilities of death from table 2 of Stover (2002, 19). The greater pessimism of the UNAIDS assumptions in the outer years is probably due to the use of a Weibull function rather than the log-logistic function.

