# CD4 Model of HIV and ART in Spectrum

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## Background

Early versions of Spectrum modeled the progression from new HIV infection to AIDS death in the absence of treatment as a single Weibull function that described the proportion dying by time since infection. The need for treatment was estimated as those within three years of death.



Recent versions of Spectrum have separated progression into two steps:

* Progression from new HIV infection to need for treatment
* Progression from need for treatment to AIDS death in the absence of treatment

Separate Weibull progression patterns for each step were developed such that the median time to need for treatment was 8 years and the overall progression to from infection to death matched the data from the ALPHA network of cohort studies[[1]](#footnote-1).



This approach worked well as long as the criterion for eligibility for treatment did not change. Once programs started changing eligibility from counts under 200 CD4 cell/μl this approach no longer worked well. We did develop alternative patterns for eligibility at 250 and 350. However this approach did not work well when switching from one pattern to the next. Although Spectrum could easily calculate the number of people in need under the new criteria, those newly in need because of the change in criteria were exposed to an immediate risk of death, whereas they had no chance of death under the old criteria until they progressed to need. As a result the number of deaths increased when the eligibility criteria changed.

## CD Model for Estimating Need for Treatment and Progression to AIDS Death

In response to these issues we have switched to a CD4 compartment model. The major advantage of this approach is that the number of people eligible for treatment can easily be determined at any point in time based on the CD4 level for eligibility. Mortality is not be affected by changes in criteria and the eligibility criteria can change many times during a projection.

The model structure has seven CD4 compartments as shown below. The compartments were selected on the basis of eligibility criteria and mortality patterns. To match eligibility criteria in use today we needed categories for <200, <250 and <350. Since mortality patterns for untreated patients are very different for those <50 and <100 we split the <200 category into <50, 50-99, and 100-199.

The model tracks the HIV+ population by CD4 count using an approach similar to one used in South Africa recently to estimate the need for treatment[[2]](#footnote-2) (see Figure 1). We assume that most newly infected people start with CD4 counts above 500, although some portion, p, can start at 350-499. The transition probabilities λ1, λ2, λ3, λ4, λ5 and λ6 represent the probability of progressing from one CD4 category to the next. In each category there is some probability of death from HIV-related causes, designated as μ1, μ2, μ3, μ4, μ5, μ6 and μ7 as well as a chance of death from non-AIDS causes, μ0 (not shown in the figure). The probability of HIV-related death increases as CD4 counts decrease.

The number of people in the different CD4 count categories represents the HIV-infected population that is not on ART. The number of people eligible for treatment is the number in each CD4 count category that is below the recommended level for initiating ART.

Depending on the eligibility criterion and the level of first line ART coverage, a percentage of those eligible for treatment will start first line ART (c1, c2, c3, c4, c5, c6, c7). Those on ART are categorized by their CD4 count at the initiation of treatment. The model does not track the temporal decline of CD4 counts of those on treatment. Those on first line ART have a probability of failure depending on their CD4 count at initiation, α1, α2, α3, α4, α5, α6 and α7.

The number starting ART each year is determined by the assumed coverage and the number of people in the eligible for treatment. We assume that those starting on ART will be distributed among the eligible CD4 categories such that an equal percentage of people in each eligible CD4 category initiate treatment.



## Specifying Model Parameters

We have specified that parameter values for the model by starting with values in the published literature and then fitting the model to data from the ALPHA network. Progression from infection to death is slower for young people than older people. The ALPHA network analysis1 found a median time from infection to AIDS death of 12.8 years for those aged 15-24, 10.6 years for 25-34, 7.5 years for 35-44, and 56 years for 45+. They found no difference by sex once survival was adjusted for age. We have used these data to develop parameter sets for these four age groups.

A recent publication by Johansson *et al.* summarizes data from 6 countries on mortality by CD4 count for those not on ART[[3]](#footnote-3). They found annual mortality of 0.8 (0.7-0.9) for those with CD4 counts <50 (from one study in Thailand), 0.355 (0.335-0.375) for those with CD4 counts between 50 and 199 from 6 studies, and 0.109 (0.093-0.125) for those with CD4 counts between 250 and 350 from six studies.

Information on the rate of CD4 cell count decline is available from a several studies, with one providing declines by CD4 category (Table 1).

Table 1. Annual declines in CD4 count among HIV-positive adults

|  |  |
| --- | --- |
| **Study** | **Annual Rate of Decline in CD4 Count** |
| CASCADE, Wolbers et al.[[4]](#footnote-4) | 61 (46-81) Fixed effects  74 (31-145) By patient  114 (32-229) Last 2 tests |
| MACS, Mellors et al. JAMA, 2007[[5]](#footnote-5) | 64 (8-136) |
| CNICS, SFMHS, REACH, Rodriguez et al.[[6]](#footnote-6) | 50 (46-55) |
| Williams et al. JID, 2006[[7]](#footnote-7) | 85 South Africa  65 Zambia |
| Cape Town, Holmes et al.[[8]](#footnote-8) | >500: 47 (40-54)  351-500: 31 (23-38)  201-350: 20 (14-27) |

For this model the parameter values were determined by using the literature values as a starting point and fitting the model to Weibull curves of progression to mortality by age from the ALPHA network. We assumed that the rate of CD4 decline is constant across all categories and that mortality varies by CD4 category but not by age. The resulting parameter values are shown in Table 2.

Table 2. Parameters for the CD4 Category Model

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Indicator** | **Age Group** | | | |
|  | **15-24** | **25-34** | **35-44** | **45+** |
| Proportion progressing out of >500 category annually | 0.125 | 0.144 | 0.253 | 0.405 |
| Rate of CD4 count decline (cells/µl) | 45 | 62 | 98 | 59 |
| Mortality <50 cells/µl | 0.44 | 0.44 | 0.44 | 0.44 |
| Mortality 50-99 cells/µl | 0.30 | 0.30 | 0.30 | 0.30 |
| Proportion of new infections starting at 350-499 | 0.20 | 0.20 | 0.20 | 0.20 |
| Median time from infection to AIDS death (years) | 12.8 | 10.6 | 7.5 | 5.6 |

Mortality while on ART has been estimated by the IeDEA (International Epidemiologic Database to Evaluate AIDS) Consortium which has analyzed data from 50,000 patients in East Africa to determine mortality of patients on ART by CD4 count at treatment initiation. In the future, mortality patterns will become available for other regions: southern Africa, West Africa, Latin America and Asia. The overall pattern of mortality by CD4 count and age is shown in Figure 2. The actual patterns used in Spectrum vary by age, sex and time on ART: 0-6 months, 7-12 months and more than 12 months as shown in Table 3.



Table 3. Annual Mortality on ART

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **CD4 Count by Time on ART** | **Males** | | | | **Females** | | | |
| **0-6 Months** | 15-24 | 25-34 | 35-44 | 45+ | 15-24 | 25-34 | 35-44 | 45+ |
| >500 | 5.84 | 4.42 | 3.91 | 4.40 | 4.22 | 3.19 | 2.82 | 3.18 |
| 350-500 | 10.53 | 7.97 | 7.05 | 7.93 | 7.61 | 5.76 | 5.09 | 5.73 |
| 250-349 | 14.33 | 10.85 | 9.59 | 10.79 | 10.35 | 7.83 | 6.93 | 7.80 |
| 200-249 | 11.13 | 8.43 | 7.45 | 8.38 | 8.04 | 6.09 | 5.38 | 6.06 |
| 100-199 | 12.78 | 9.68 | 8.55 | 9.63 | 9.23 | 6.99 | 6.18 | 6.95 |
| 50-99 | 22.74 | 17.21 | 15.22 | 17.13 | 16.42 | 12.43 | 10.99 | 12.37 |
| <50 | 41.69 | 31.56 | 27.90 | 31.40 | 30.11 | 22.79 | 20.15 | 22.68 |
| **7-12 months** |  |  |  |  |  |  |  |  |
| >500 | 1.76 | 1.17 | 1.19 | 1.42 | 1.17 | 0.78 | 0.80 | 0.95 |
| 350-500 | 2.36 | 1.57 | 1.60 | 1.91 | 1.58 | 1.05 | 1.07 | 1.28 |
| 250-349 | 2.16 | 1.44 | 1.47 | 1.75 | 1.44 | 0.96 | 0.98 | 1.17 |
| 200-249 | 1.72 | 1.14 | 1.16 | 1.39 | 1.15 | 0.76 | 0.78 | 0.93 |
| 100-199 | 2.11 | 1.40 | 1.43 | 1.71 | 1.41 | 0.94 | 0.96 | 1.14 |
| 50-99 | 2.70 | 1.80 | 1.83 | 2.19 | 1.81 | 1.20 | 1.23 | 1.46 |
| <50 | 3.43 | 2.28 | 2.33 | 2.78 | 2.29 | 1.52 | 1.56 | 1.86 |
| **>12 months** |  |  |  |  |  |  |  |  |
| >500 | 1.08 | 0.72 | 0.74 | 0.88 | 0.73 | 0.48 | 0.49 | 0.59 |
| 350-500 | 1.45 | 0.97 | 0.99 | 1.18 | 0.97 | 0.65 | 0.66 | 0.79 |
| 250-349 | 1.33 | 0.89 | 0.90 | 1.08 | 0.89 | 0.59 | 0.60 | 0.72 |
| 200-249 | 1.06 | 0.70 | 0.72 | 0.86 | 0.71 | 0.47 | 0.48 | 0.57 |
| 100-199 | 1.30 | 0.87 | 0.88 | 1.05 | 0.87 | 0.58 | 0.59 | 0.71 |
| 50-99 | 1.67 | 1.11 | 1.13 | 1.35 | 1.11 | 0.74 | 0.76 | 0.90 |
| <50 | 2.12 | 1.41 | 1.44 | 1.71 | 1.42 | 0.94 | 0.96 | 1.15 |

## Allocation of New ART Patients by CD4 Count

The number of people on ART in each year is an input to Spectrum. It is used to determine the number of people newly starting ART in each year. New ART patients need to be allocated across CD4 categories. Information from treatment cohorts on the distribution of new patients by CD4 count is based on a time when almost all countries defined eligibility for treatment as those with CD4 counts under 200. As most countries are now moving to the new WHO guidelines as <350, past patterns may not indicate future patterns.

We have considered two options for allocating new ART patients by CD4 count:

1. Start the same proportion on ART from each eligible CD4 category
2. Allocate new ART patients on the basis of expected AIDS mortality without ART.

When comparing the two methods with data from southern Africa treatment sites it appears that the first method (allocating an equal proportion from all eligible CD4 categories) tends to under-estimate the number starting at low CD4 counts and over-estimate those starting at higher CD4 counts. Weighting the allocations by expected AIDS mortality produced the opposite results, there are too many starting at low CD4 counts and too few at higher CD4 counts. An average of the two methods produces a pattern that matches the data reasonably well. Therefore, Spectrum calculates allocations according to both methods and averages the results.

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2. Adam MA, Johnson LF. 2009. Estimation of adult antiretroviral treatment coverage in South Africa. SAMJ September 2009: 99;9: 661-667. [↑](#footnote-ref-2)
3. Johansson KA, Robberstad B, Norheim OF. Further benefits by early start of HIV treatment in low income countries: survival estimates of early versus deferred antiretroviral therapy. *AIDS Research and Therapy*  2010, 7:3. [↑](#footnote-ref-3)
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