

Comparison of Markov and Discrete Event Simulation Models for HIV-Disease

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Objective

To compare the input data requirement and resulting estimates of various parameters for a "discrete event simulation (DES) model" to a previously published Markov model¹ in decision analysis studies for HIV-disease.

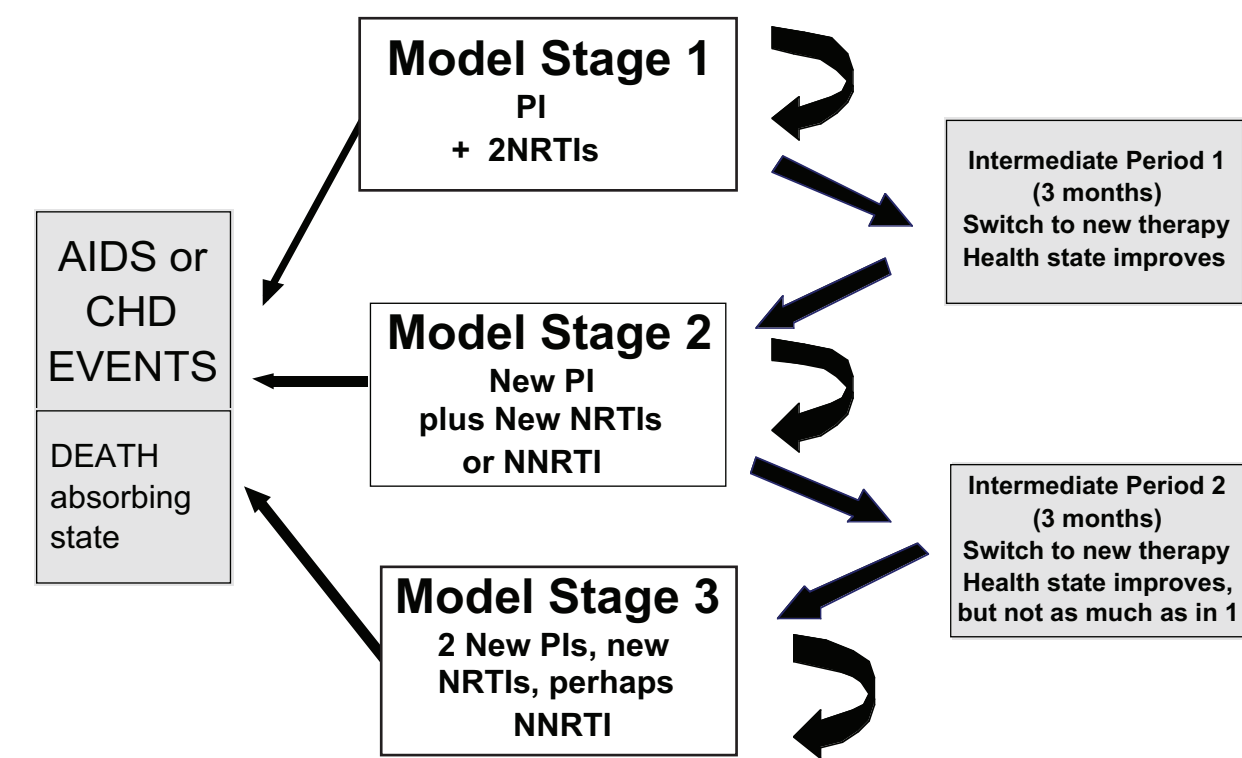
Methods

Using a known cohort of antiretroviral naïve patients³ with a mean baseline CD4+ T-cell count of 175 cells/ μ l, the DES model estimates for the different parameter values were compared to actual population values and estimates from a previously published Markov model.

Markov Model

- The model simulates outcomes (in terms of Quality Adjusted Life Years, QALYs) and costs for a cohort of patients starting on one drug regimen and compares them with those for a cohort of patients starting on another regimen.
- The structure used is a Markov model, which allows for transitions between 12 health states defined by CD4+ T-cell count and HIV-1 RNA level (viral load, VL) every 3 months². These health states capture the differential effects of VL suppression and CD4+ T-cell count increases reported in the clinical trial for each regimen on costs and QALYs. Once the time period for the clinical trial results is exhausted, health state progression is based on data from large clinical cohorts of patients on antiretroviral therapy (ART). The relationships captured in the model are shown in the figure below:

Figure 1. Schematic overview of the Markov model



CHD – Coronary heart disease

Discrete Event Simulation (DES) Model

- The DES model is structured using ARENA software from Rockwell Automation. A DES model is a mathematical structure using a stochastic process to simulate outcomes for a "synthetic" or theoretical patient cohort to capture the effects of key characteristics with varying value levels¹, such as:
 - 1) proportion with VL suppression below 50 copies/ml or between 50 and 400 copies/ml,
 - 2) treatment adherence,
 - 3) heart disease risk,
 - 4) viral resistance, and
 - 5) competing causes of mortality with advanced age.
 Using data from a known patient cohort³, the DES model estimates for the different parameter values, budget impacts and cost effectiveness estimates were compared to previously published estimates from a Markov model.

DES model structure

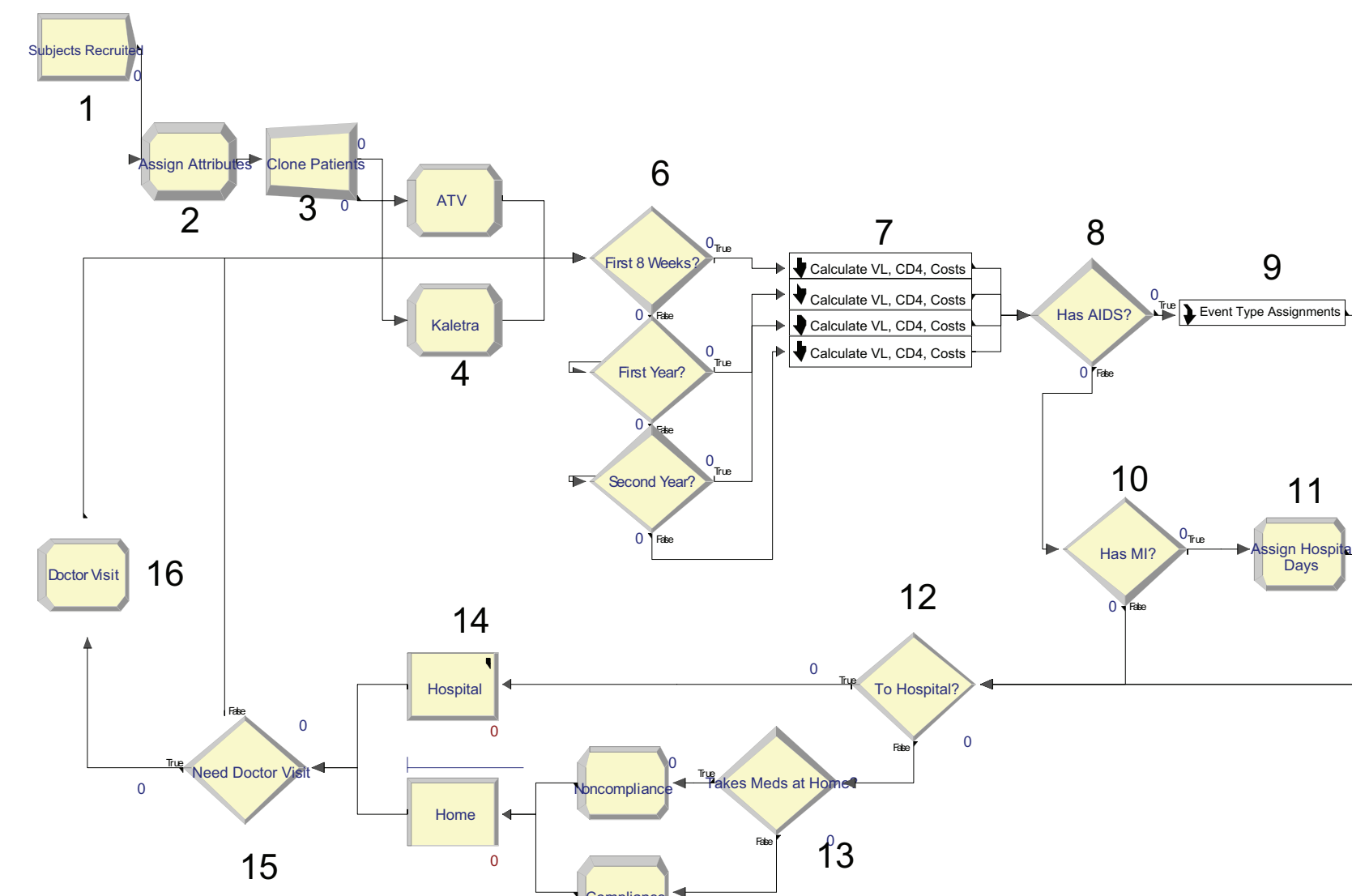
Discrete event model structure has advantages over Markov model:

- 1) It represents the course of a disease in real time, with few restrictions.
- 2) It does not require mutually exclusive branches or rigidly defined health states with fixed cycles like Markov model does.
- 3) The process of modeling follows actual treatment process and it gives a visual indication of what happens to each unit (patient) as they progress in the process. This gives the model a superior face validity with decision makers.
- 4) Most importantly, this model provides a probabilistic sensitivity analysis, which is very restrictive with a Markov model.

Methods (cont.)

The model software ARENA provides a graphic representation of the process that patients go through as they progress through the model. This model characteristic has two advantages over a Markov model structure: 1) It is useful for testing that the technical programming of the model works correctly, because patient entities can be observed visually as they pass through the process diagram, and errors can be identified visually; 2) the process diagram can be supplemented with cartoon pictures or symbols that depict what is happening to patients. This can help a lay audience better grasp the effect of treatment differences. A screen shot of the main process used in our DES model is provided below (Figure 2).

Figure 2. Kaletra Discrete Event Simulation (DES) Model—The chronological trajectory of the processes of the model with possible options at each point of decision



Kaletra: DES model

- 1) The model begins with the recruitment of subjects.
- 2) At this point, the number of patients in each treatment arm (currently 100), patient characteristics: age, sex, and baseline disease characteristics are specified. Then attributes to the recruited patients are assigned. The attributes encompass the mean values for patient characteristics: age 35.5 years, 80% male, CD4+ T-cell count 175 (SD 50), VL 100,000 (SD 20,000), antiretroviral-naïve, heart disease risk of 4.6% at 10 years. A unique combination of these values is assigned to each recruited patient in such a way that the composition of the cohort reflects the defined parameters. These baseline parameters can be changed easily by inserting new values for the baseline variables into the model.
- 3) After subjects are "recruited" or defined in the model by the means and the standard deviations of the baseline variables and distributions appropriate for the baseline parameters, the model "clones" all patients. This step is performed to assure that the model uses an identical patient cohort for the treatment and the comparison regimen in each run.
- 4) At this point the cloned patients are labeled as belonging to the comparison group, and the original cohort as belonging to the treatment group.

The process which occurs in steps 1–4 has no time dimension, it is assumed to be instantaneous.

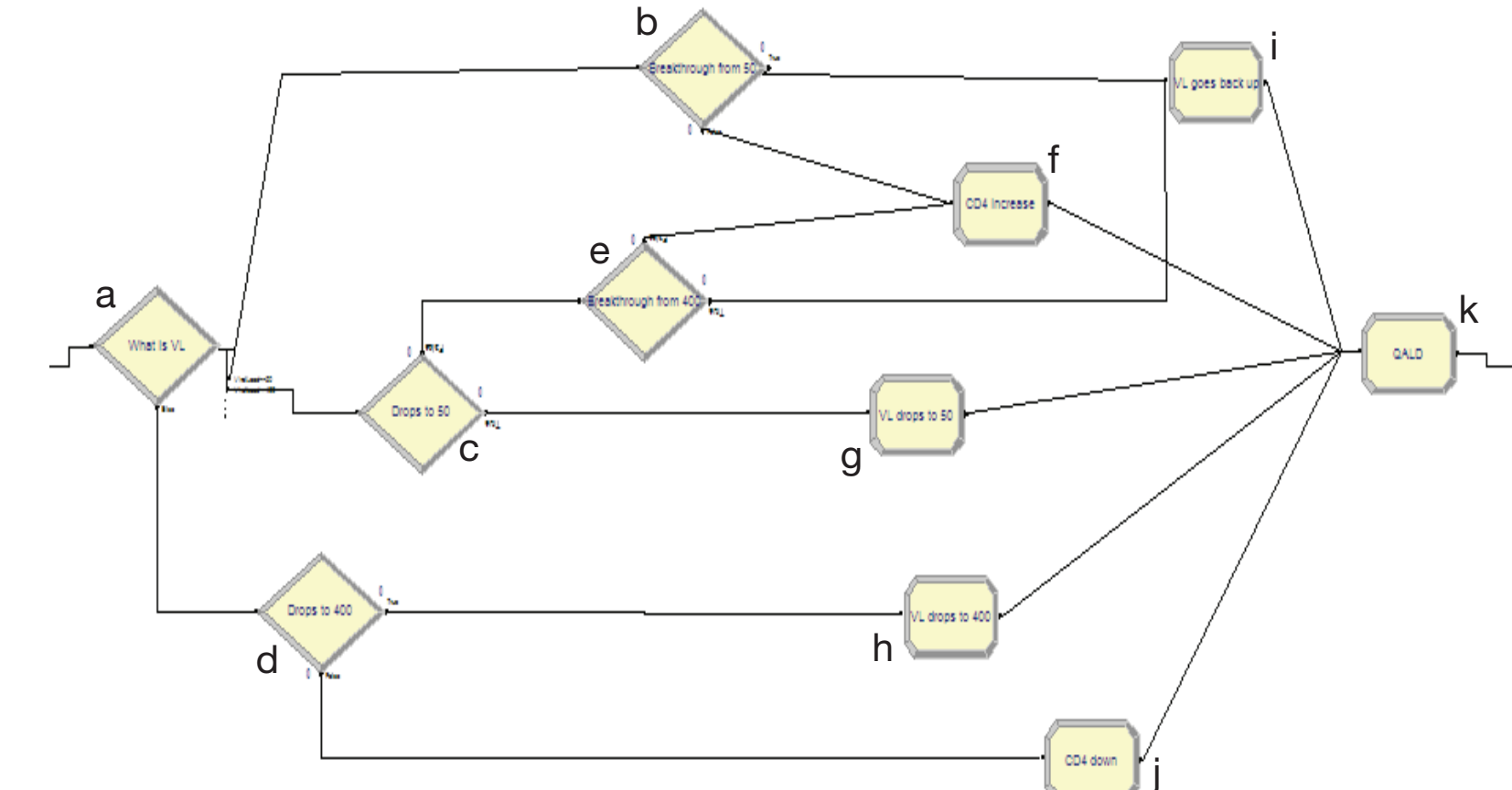
The model is not limited to a single process, but can with ease contain many sub-processes. In our HIV-disease model the changes in viral load (VL) and CD4+ T-cell counts, and the risks of getting an AIDS event is built as a separate process into the model. Other separate processes include: one for estimating antiretroviral impacts (at 8 weeks, 48 weeks, 2 years and more than 2 years), an ACUTE AIDS treatment process, a Medical Visit Monitoring Process, and separate processes for switching to subsequent salvage regimens after the initial regimens fail. A screen shot of the VL and CD4+ T-cell count assignment process is depicted below.

After steps 1–4 are complete, each individual goes through the process of the main model and time-dependent sub-model shown in Figure 3 each time (s)he goes through evaluation; thus every day of his/her life is evaluated as to how much quality of life was affected for that particular day based on VL, and CD4+ T-cell count, and how much cost was added to the liability.

Methods (cont.)

One of the sub-models also evaluates incidence/risk of AIDS-related events including cardiovascular events (Figure 3) and the information is translated into costs and QALDs (Quality-Adjusted Life Days). The model continues to update VL, and CD4+ T-cell count, and aggregates the costs and QALDs at the end of every day so that the statistics will be updated at any point in time.

Figure 3. Time-dependent Sub-model Structure—The chronological Trajectory of possible events in terms of viral load, and CD4+ T-cell count and their effects on Quality-Adjusted Life Days (QALDs)



The process will be repeated for as many treatment arms and comparator groups as there are, and resulting statistics will be provided.

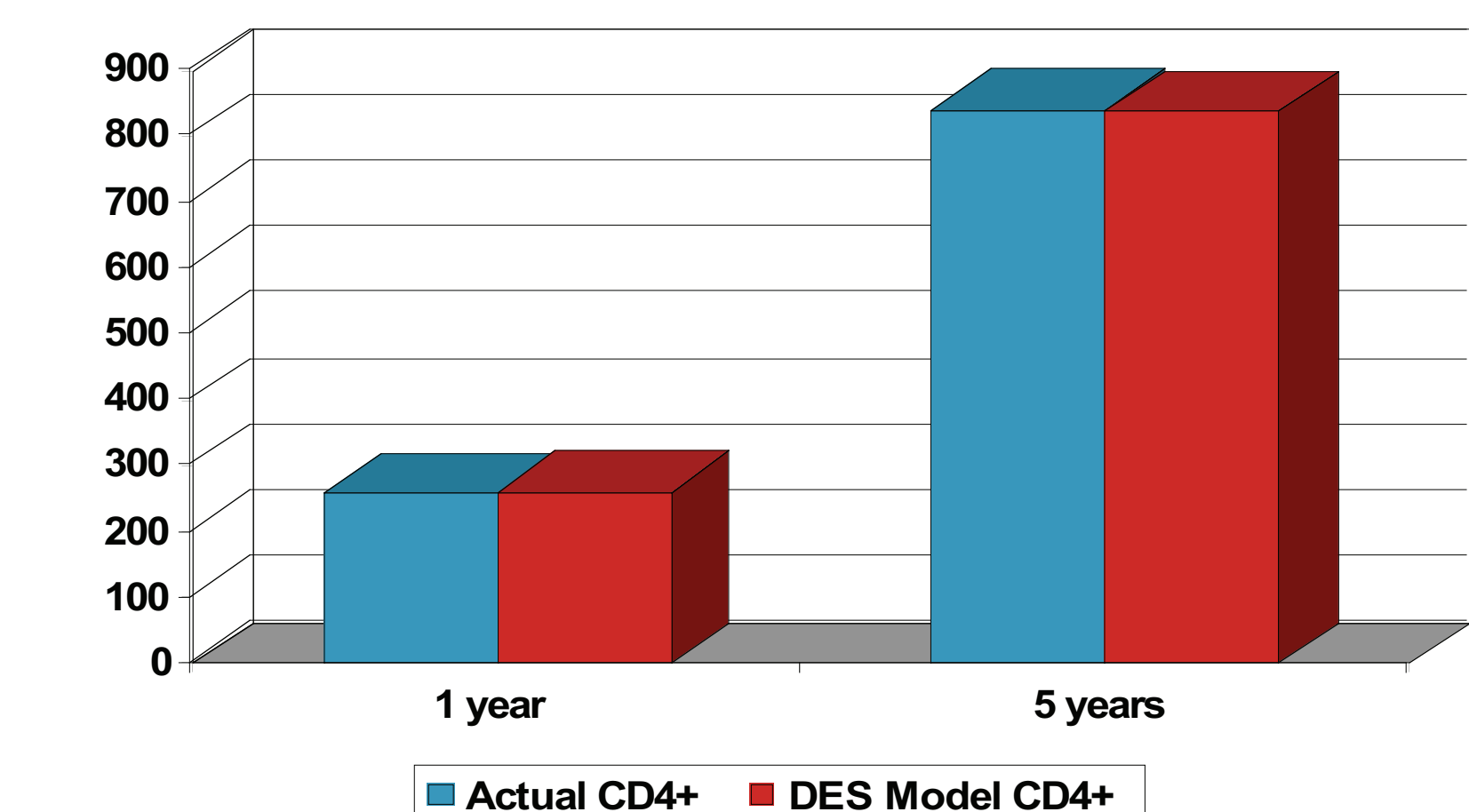
Based on these statistics, an economic analysis is undertaken.

DES Model's Special Use of Statistical Parameters

A Markov model uses mean values for all the variables in the model to calculate outcomes, while a DES model uses a random draw from the distributions depicted by mean values and their measures of variation to estimate outcomes. Thus, DES outcomes are always estimated a number of times and the mean of these estimates are reported. This provides some information about the effect of the statistical uncertainty in the model input values. Stable models that are based on strong statistical parameters will show little variation in the estimates, while unstable model estimates will vary greatly. Examining the high and low values for each parameter gives the audience a good idea of the stability of a model. The following slides show that the 1- and 5-year estimates of CD4+ T-cell count and VL from our DES model are very stable, and lie very close to the values actually observed in the cohort underlying the model.

Results

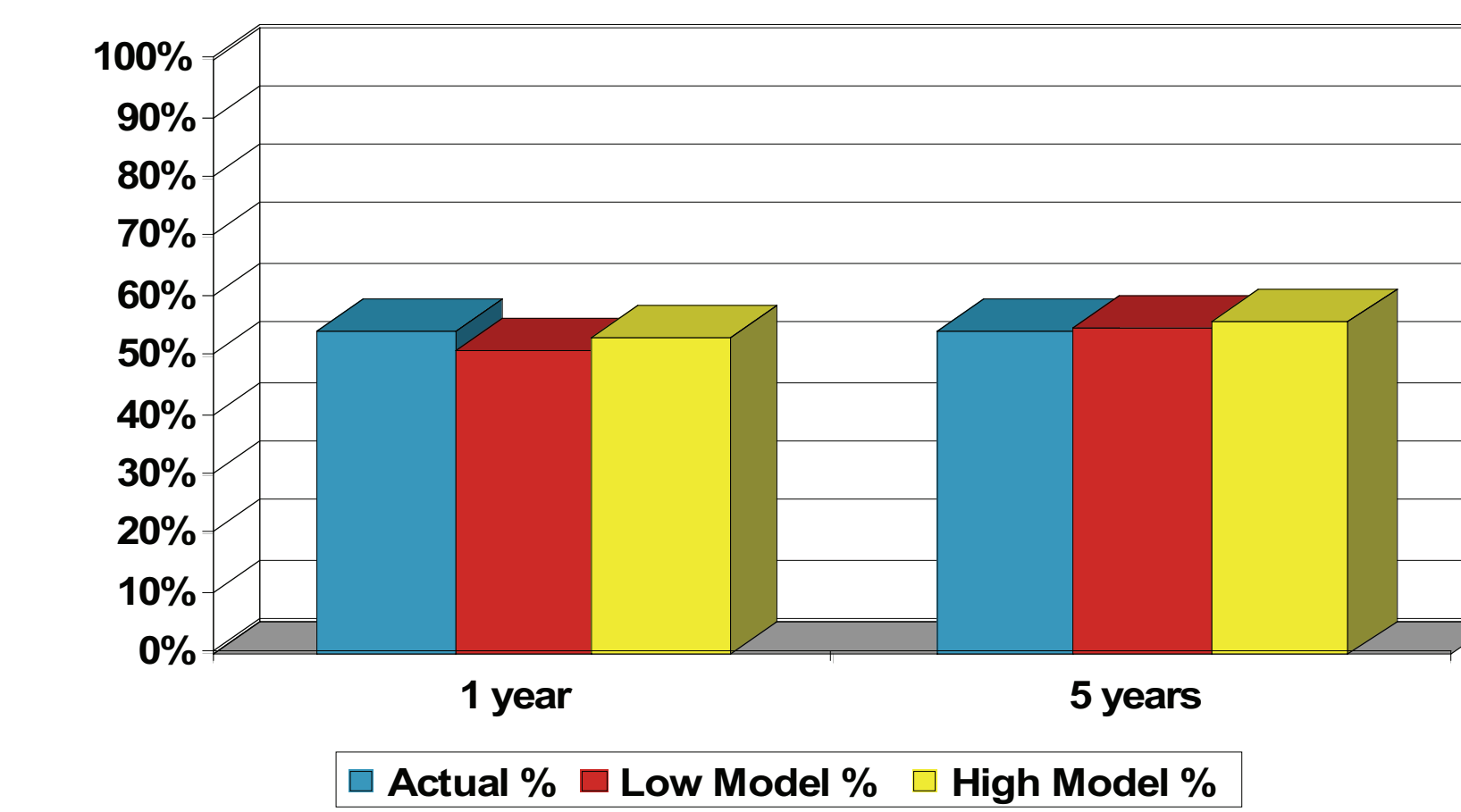
Figure 4. Cohort Mean CD4+ T-cell count—Value obtained from DES model iterations* compared to actual value from the clinical trial data



*Markov model results cannot be estimated for these values.

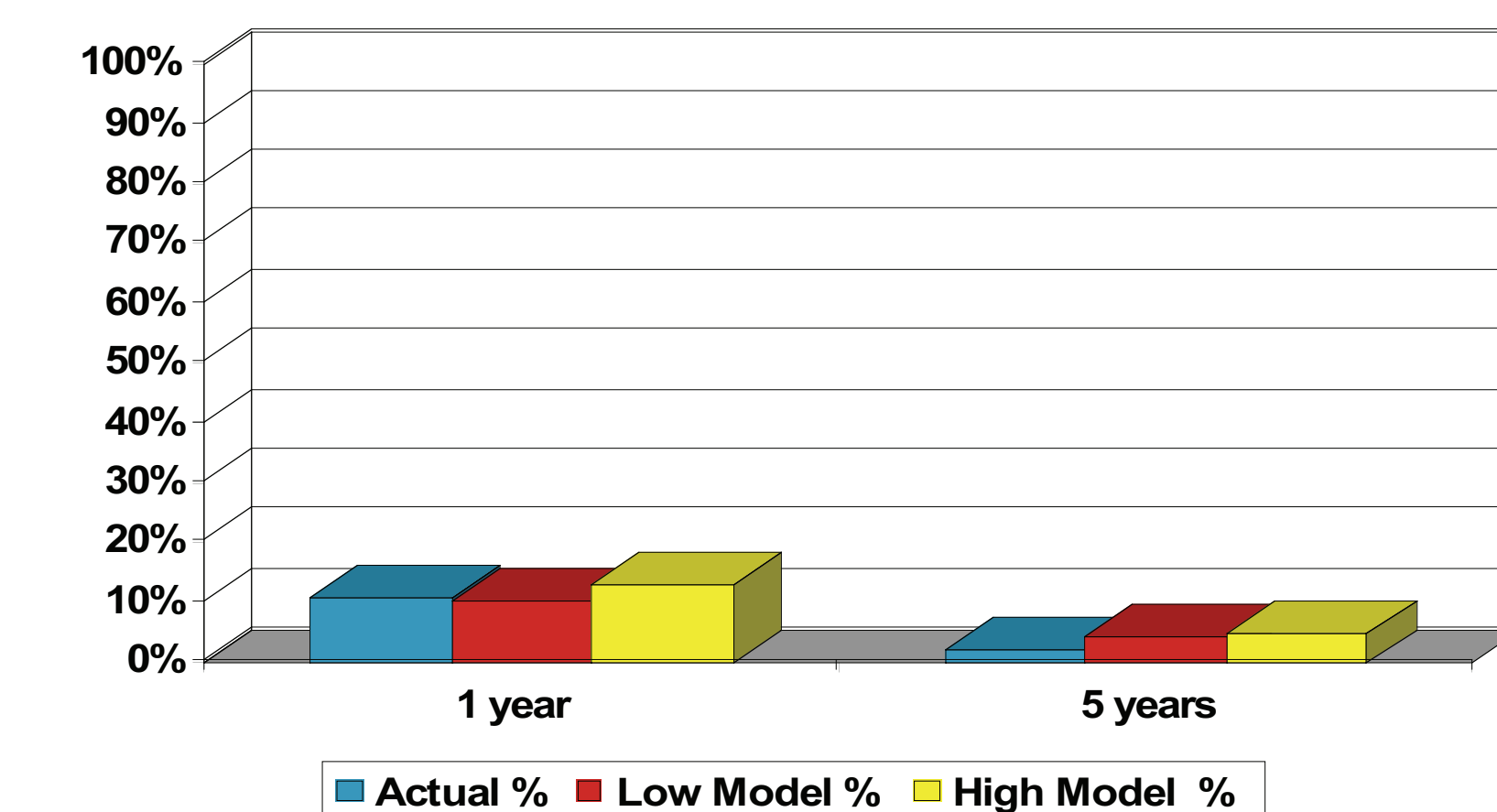
Results (cont.)

Figure 5. Percent VL <50 Copies/ml for the cohort—High- and Low-end estimates of the range obtained from DES model iterations* compared to actual value from the clinical trial data



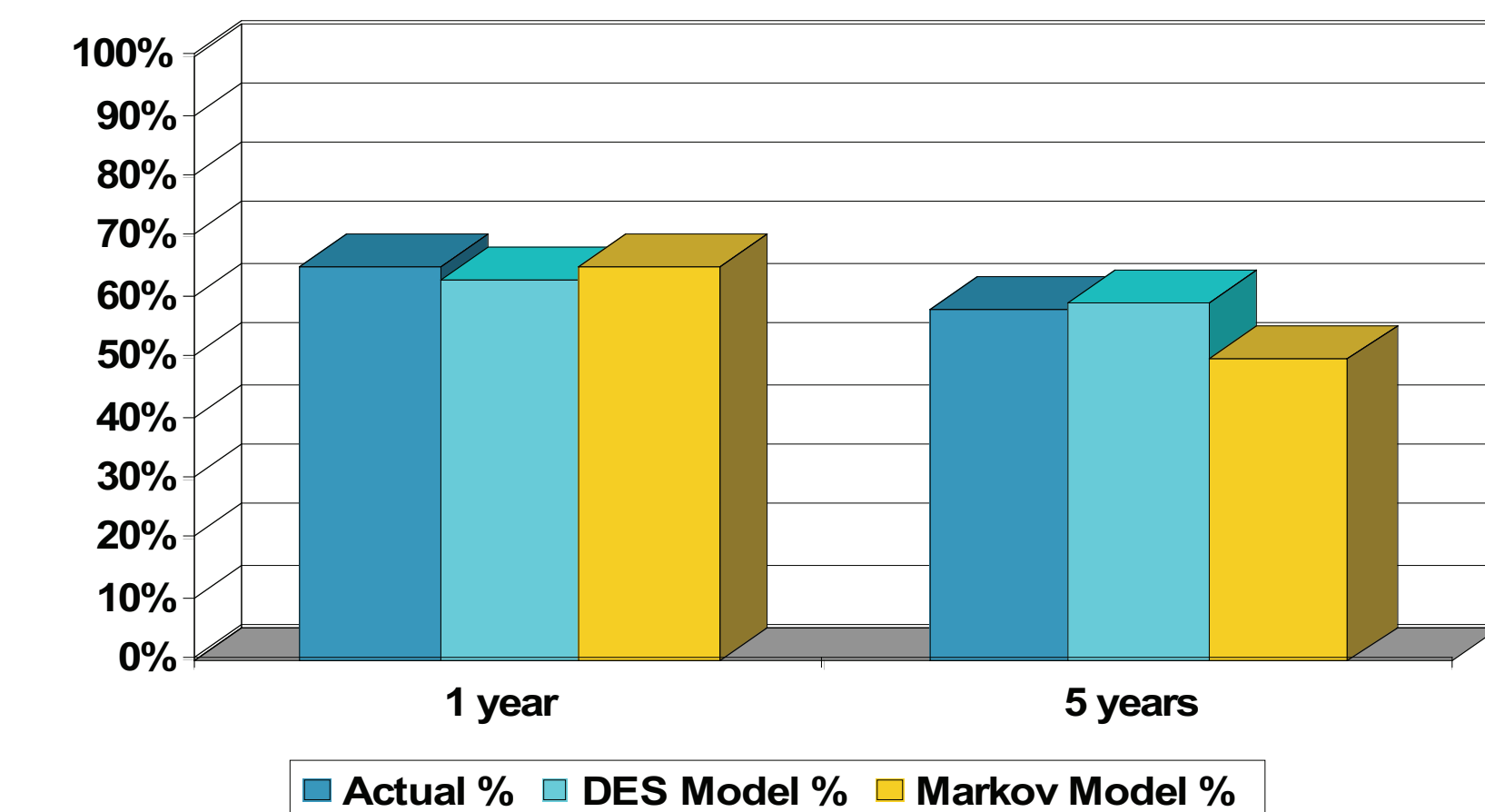
*Markov model results cannot be estimated for these values.

Figure 6. Percent <50<VL<400 copies/ml for the cohort—High and Low end of the range obtained from DES model iterations* compared to actual value from the clinical trial data



*Markov model results cannot be estimated for these values.

Figure 7. Percent Population VL <400 copies/ml vs. DES and Markov Model Estimates*



Comparison of DES model to Markov model (Figure 7)

Results of both DES and Markov models are similar when the timeframe of reference is shorter (1 year).

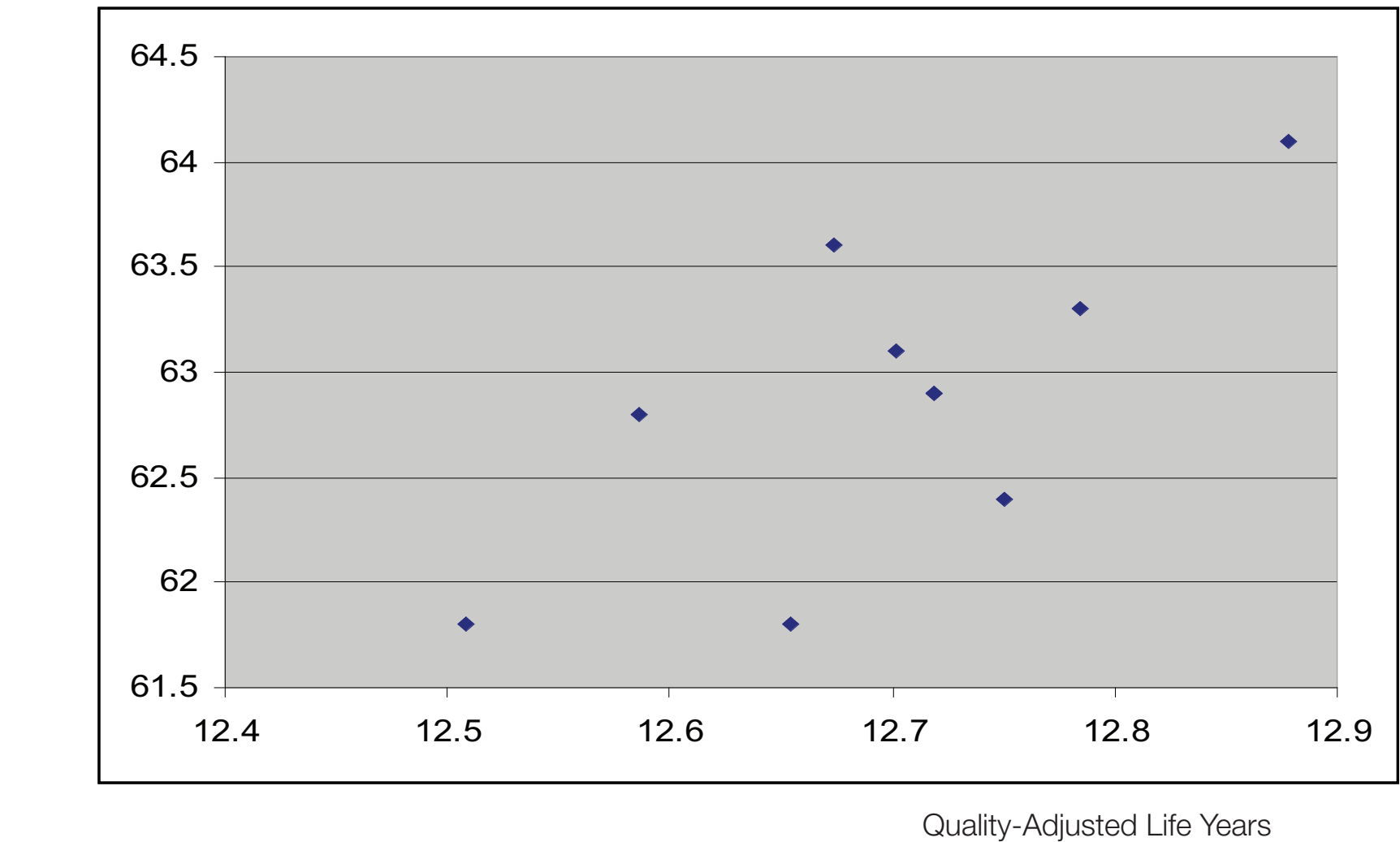
On the other hand, results at the end of a longer duration (5 years) show that DES model has much better predictive ability than the Markov model.

Probabilistic Sensitivity Analysis (PSA) and evaluation of correlation between VL and QALYs

A DES model can be programmed to perform 100 estimates, each based on a randomly selected combination of the model variables, as specified by the values and distributions of the parameters of the model. Each estimation can be set for a specific cohort size. This allows the user to perform probabilistic sensitivity analysis, as well as examine the effects of applying model decisions to small and large practice settings.

In addition, this probabilistic feature allows the user to plot the relationships between key model outputs to get an understanding of how outputs and variable values move together. This facility is illustrated in Figure 8 below where the estimated 48-week VL value and the corresponding average patients survival estimates are plotted together. This plot makes it very clear that these two outcomes are correlated as expected.

Figure 8. Correlation Between Model Predictions of 48 Week VL and Survival Estimates VL <400



Results

The discrete event model predicts more detailed outcomes and has better long-term predictive validity than the Markov model. It represents the course of a disease naturally, with few restrictions. This gives the model superior face validity with decision makers. Most importantly, this model automatically provides a probabilistic sensitivity analysis, which is cumbersome to perform with a Markov model.

Conclusions

- Due to the limitations of the Markov model, researchers end up using categorical groupings for complex interacting continuous measures with a potential for short-term aggregation bias leading to long-term prediction errors. Discrete Event models allow inclusion of individual variables without a need for creating compound health states, thus improving the model precision as demonstrated above.

References

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2. Simpson KN, Luo MP, Chumney EC, King MS, Brun S. Cost-effectiveness of Lopinavir/Ritonavir Compared with Atazanavir in Antiretroviral-Naïve Patients. *Clin Drug Invest* 2007; 27(1): 67-74.
3. Hicks C, King MS, Gulick RM, et al. Long-term safety and durable antiretroviral activity of lopinavir/ritonavir in treatment-naïve patients: 4-year follow-up study. *AIDS* 2004; 18:775-779.