ISPOR-SMDM

Conceptualizing a Model: Supplementary Material

A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-2

Examples of problem and model conceptualization: the case of HIV disease

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Abstract: We will use a series of examples in HIV disease to illustrate the components of good modeling practices. First, a broad conceptualization of HIV disease will be described, using an influence diagram approach, which might be the result of a process to conceptualize the problem being evaluated. Then, various types of questions will be posed that suggest a particular modeling method, and a paper using that technique will be described, including how the particular question being asked suggests the type of model used. This is not intended to be a comprehensive review of the use of modeling in HIV disease. Rather, it is designed to describe how various components of the conceptualization of the problem lead to preferences of one modeling type over another. As noted in the body of the paper, although many modeling methods can be used to evaluate the same set of questions, some problem formulations are more suited to specific methodologies.

Developing a conceptual model of the components of HIV disease

HIV infection is a complicated disease that has biological, physiological, sociological and health system level components that affect it. HIV disease has been the subject of a large number of models from highly mechanistic models of virologic dynamics to various treatment decisions to public health strategies to control the epidemic. Figure A1 describes one of many possible conceptual models of HIV disease that could be developed in the course of modeling a particular problem.

This characterization is not meant to be complete: rather it is designed to be illustrative regarding the process of matching a conceptual model of a particular problem formulation.

Briefly, uninfected people may become infected and develop symptoms of acute HIV infection, followed by a period of time where they are asymptomatic. They then develop symptomatic HIV infection and eventually may progress to develop AIDS with potential for nosocomial infections. Either as a result of screening or through presentation with symptoms, patients may be found to have HIV disease. After diagnosis, a series of treatments may or may not be

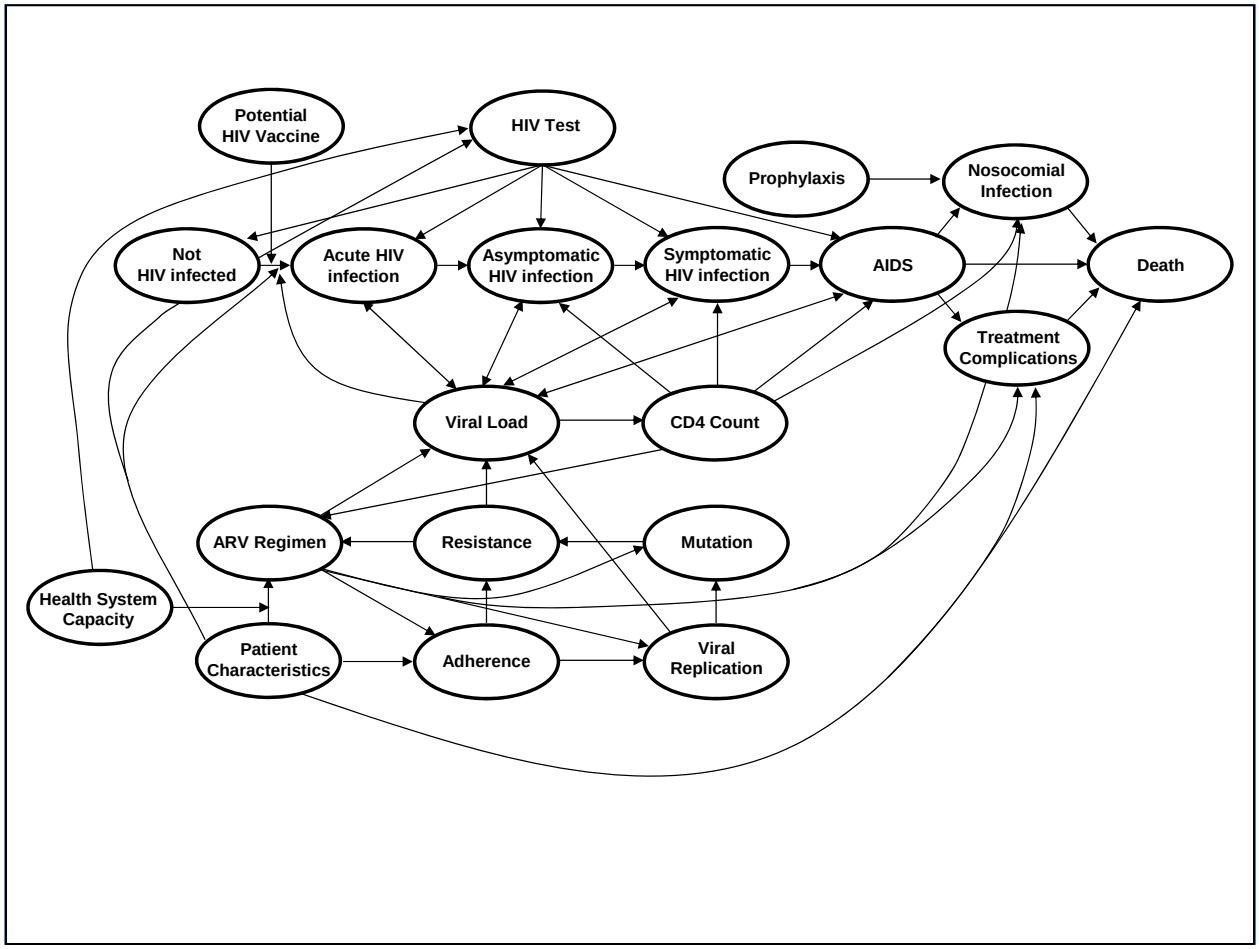

Figure A- 1 Potential conceptual model of the relationships in HIV disease. See text for details.

initiated. Treatments provide substantial benefit, and change the biological picture of the disease by changing viral load and CD4 count, but also sometimes produce complications. Eventually all patients will die, whether or not they are on treatment. The disease can be characterized by multiple parameters. In this particular illustration the disease is characterized by viral load and CD4 count. Viral load is primarily affected by whether the patient is on an antiviral regimen and whether the particular virus has developed a resistance to that series of medications. At a more biological level, resistance develops through the combination of viral replication and

mutation in the presence of selection pressure from a particular antiretroviral (ARV) regimen. Viral replication and ARV effectiveness is partially determined by adherence. Patient characteristics such as demographics, comorbid disease, socio-economic status, and many factors may affect a series of other components of the model, including causes of death, treatment complications, the likelihood of transmission and the decision to start an antiretroviral therapy. The disease can be known or unknown, the presence of the disease in a person or group can be determined through the use of the HIV test. The capacity of the health system may affect the ability to screen, make diagnoses and treat all those individuals whom would benefit by treatment. Future potential therapies, such as a potential HIV vaccine, could change the likelihood of transition from not HIV infected to Acute HIV infection.

Model using a basic decision tree

The complexity of HIV disease has made the use of a basic decision tree uncommon in the evaluation of diagnostic or treatment strategies. However, there are several examples of simple decision trees used early in the evaluation of the epidemic. Johanson evaluated three different diagnosis and management strategies for the treatment of acute diarrhea in patients with AIDS.(1) The authors could use a standard decision tree as the outcomes evaluated were relatively short-term (a short time horizon), and the long-term effects (survival) were assumed to be unchanged by the treatment of the diarrheal illness. The consequences of the decision (successful or failed diagnosis and treatment) occur within that short time frame, and the results of the decision affected only these short term outcomes.

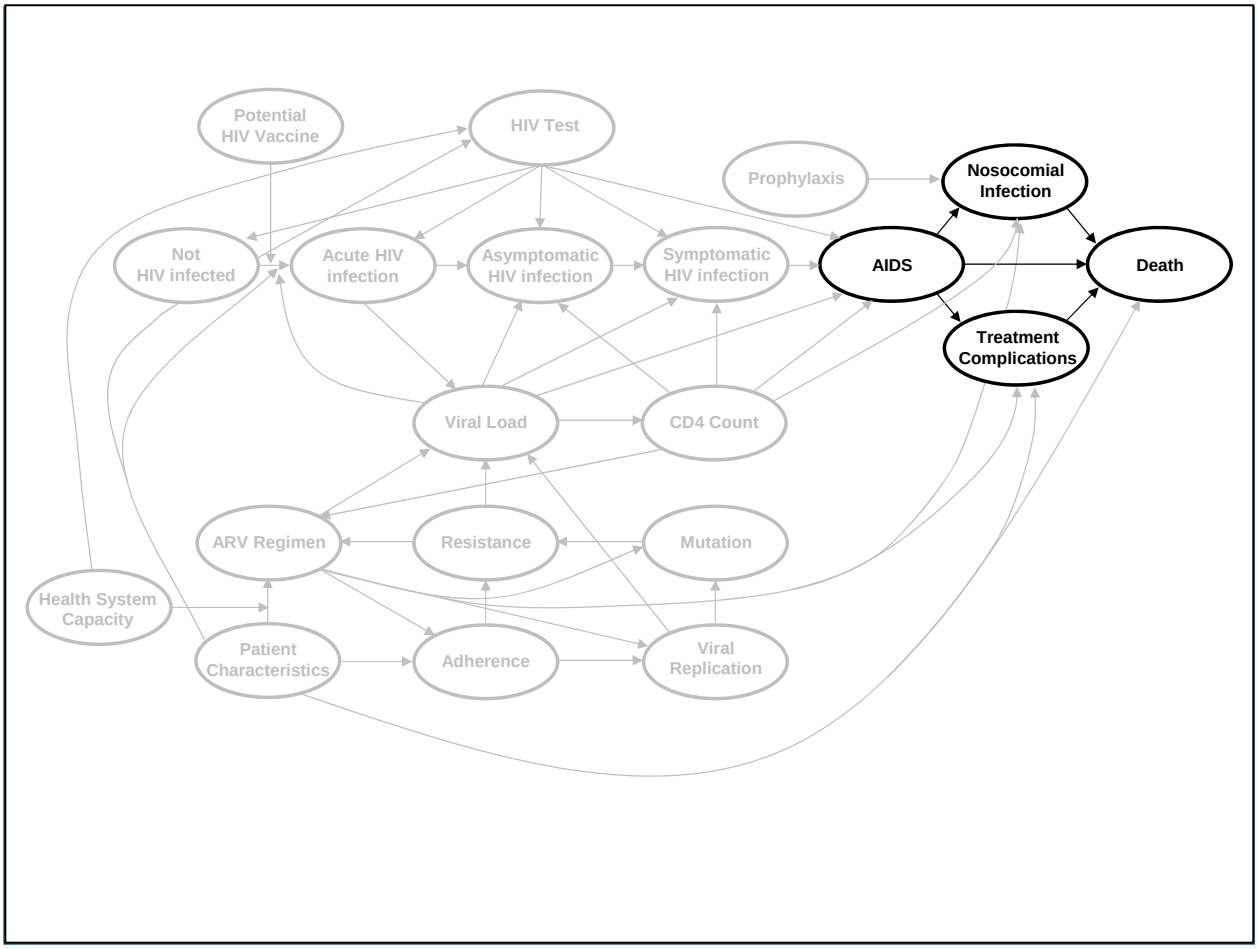

Figure A- 2 Components of the HIV conceptual model incorporated into the decision tree model of Johanson, which evaluated treatment strategies of a nosocomial diarrheal illness in patients whom already had AIDS. Infection and the epidemic, disease progression, primary HIV treatment was not considered. Outcomes beyond the treatment of the acute illness were assumed to be equivalent across decisions.

With these assumptions, the decision problem examines a very small component of our conceptual model of HIV disease, which would be a characteristic of problems appropriate for a simple branch and node decision tree. (Figure A2)

Model using a cohort based state transition model (see paper 3 for details)

As treatment for HIV disease improved in the early 1990's, the impact of improved treatment on the benefits to screening various populations was unknown.

Sanders et al developed a Markov model to investigate the costs, outcomes and cost-effectiveness of various screening strategies in the presence of highly active antiretroviral therapy.(2)

Examining our conceptual model of HIV disease we can modify the figure to eliminate the components not directly applicable to this particular problem. Because screening programs are designed to find people who are asymptomatically infected, this model ignores the development of HIV infection in patients who are currently HIV-negative, and also ignores evaluation of treatment of the acute infection (Figure A3).

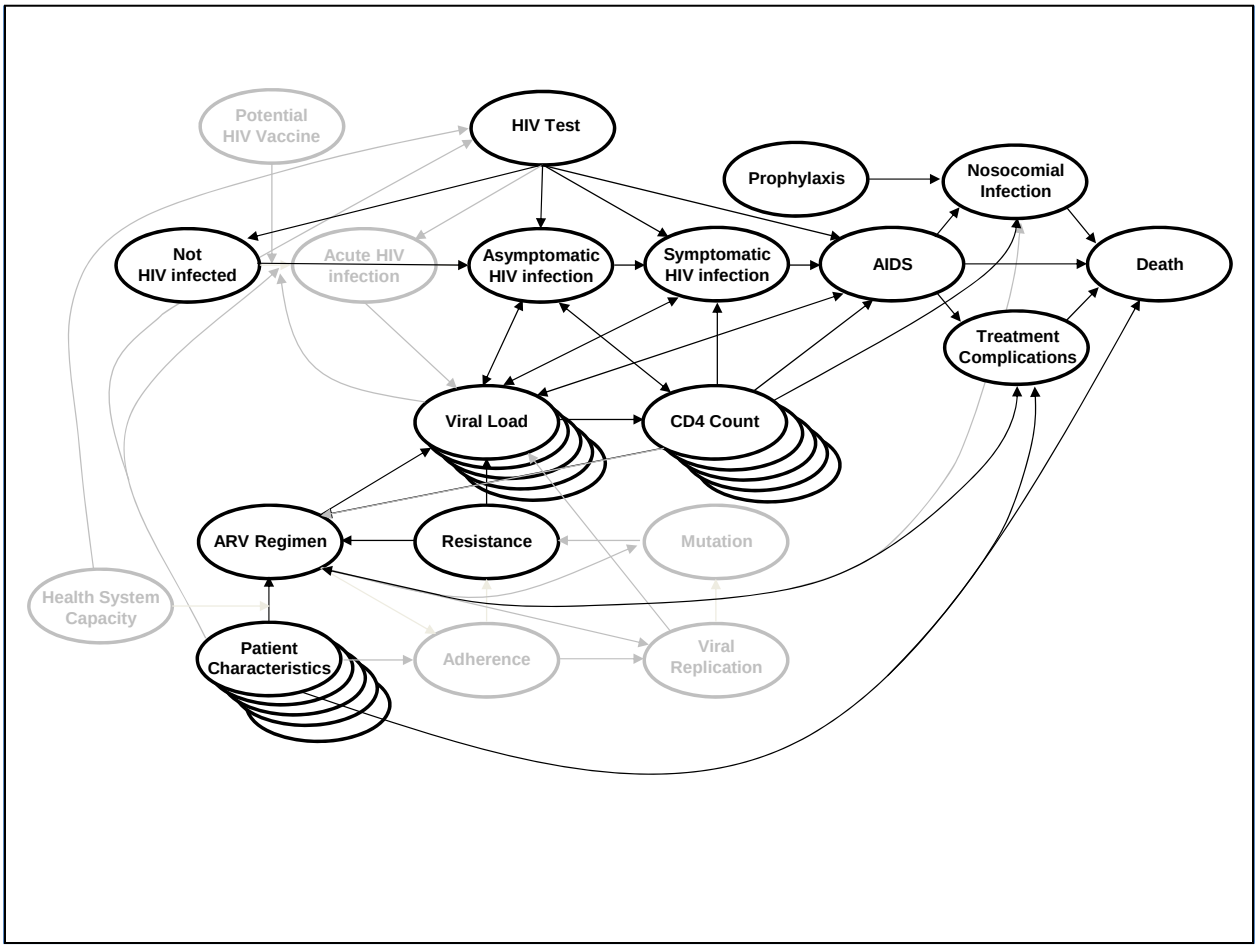

Figure A- 3 Components of the HIV conceptual model incorporated into the state transition model of Sanders, which examined the cost effectiveness of screening for HIV disease. Patients were described in multiple categories of clinical characteristic, CD4 count and viral load, and there was and various screening strategies were applied to a cohort of patients with a mix of infected and uninfected individuals, but the transition between uninfected and infected was simply measured as a probability, avoiding the need for a dynamic transmission model. The model eventually contained several hundred states, which approached a limit of tractability.

Similarly, although the model they developed incorporates multiple cycles of therapy, the success of therapy, and the development of resistance, all of these events are modeled probabilistically in the component of the model that represents the treatment of HIV disease. The main components of the model involved case finding, and therefore the representation of the treatment phase of HIV disease is relatively straightforward and is characterized by average rates of virological suppression by cycle of therapy. The specifics of each regimen, i.e. the particular medications chosen, are not explicitly modeled. Similarly specific treatments for nosocomial infections are not explicitly modeled.

Because each of the components of the disease is treated somewhat categorically, (for example the states of disease and treatment are only characterized by levels of CD4 count, viral load, and treatment regimen) the model can be constructed as a Markov process, and evaluated as a cohort simulation.

The model has a partial consideration of the impact of HIV disease and treatment of HIV disease on transmission. Although it is not designed specifically to examine the impact of screening on the epidemic, it does allow for infected individuals to transmit their disease to uninfected individuals at rates proportional to their age, viral load and several other factors. It is necessary to do this to understand the impact of screening and treatment on the number of individuals that each patient may in fact which increase the cost and burden of the disease.

Models using an individual microsimulation state transition model (see paper 3 for details)

One of the most detailed examples of a microsimulation model of HIV disease is the Cost-Effectiveness of the Prevention of AIDS Complications (CEPAC) model. (3, 4)

The model was originally designed to understand the cost-effectiveness of various strategies to treat and prevent the complications of AIDS, and was expanded to evaluate the value of triple therapy in chronic HIV disease. The model concentrates on understanding the impact of treatment on disease progression as represented by CD4 count and viral load, taking into account other patient characteristics and the development and treatment of HIV related complications

This particular use of the CEPAC model is not concerned with the development of HIV disease from patients who are currently not infected, nor is it concerned with acute or asymptomatic HIV-infected as all patients are known to be infected and are under consideration for therapy. Similarly, the early versions of the model represented the development of resistance probabilistically rather than as a direct relationship between viral replication and mutation, therefore detailed modeling of the development of antiviral resistance acquisition is not necessary.

The concentration of the model on the relationships between CD4 count viral load and the progression of HIV disease provide insights as to why modeling this particular problem as a Monte Carlo microsimulation is also appropriate. The complexity involved in the combination of regimens, resistance patterns, patient characteristics, viral load and CD4 count would require literally thousands of states if constructed as a standard cohort simulation state transition model, which is indicated by the multiple copies of the states at **CD4 Count**, **Viral Load**, and **Patient Characteristics** in figure A4.

The use of microsimulation, in which one entity passes through the model at a time, allows for a significant amount of detail to be incorporated into a series of equations that govern transitions rather than in the definition of various states. Because the model is an individual microsimulation, and tracks the characteristics of each individual who progresses through the model, the model has complete information about how long each patient has had HIV disease, what regimens they have been on, what infections they have had, and what the history of their CD4 count and viral load has been.

These characteristics are necessary to evaluate certain transition probabilities, and it is this complexity that strongly suggests that the model be constructed as a microsimulation, rather than a cohort-evaluated state transition model, which would require literally thousands of states to represent this level of clinical detail.

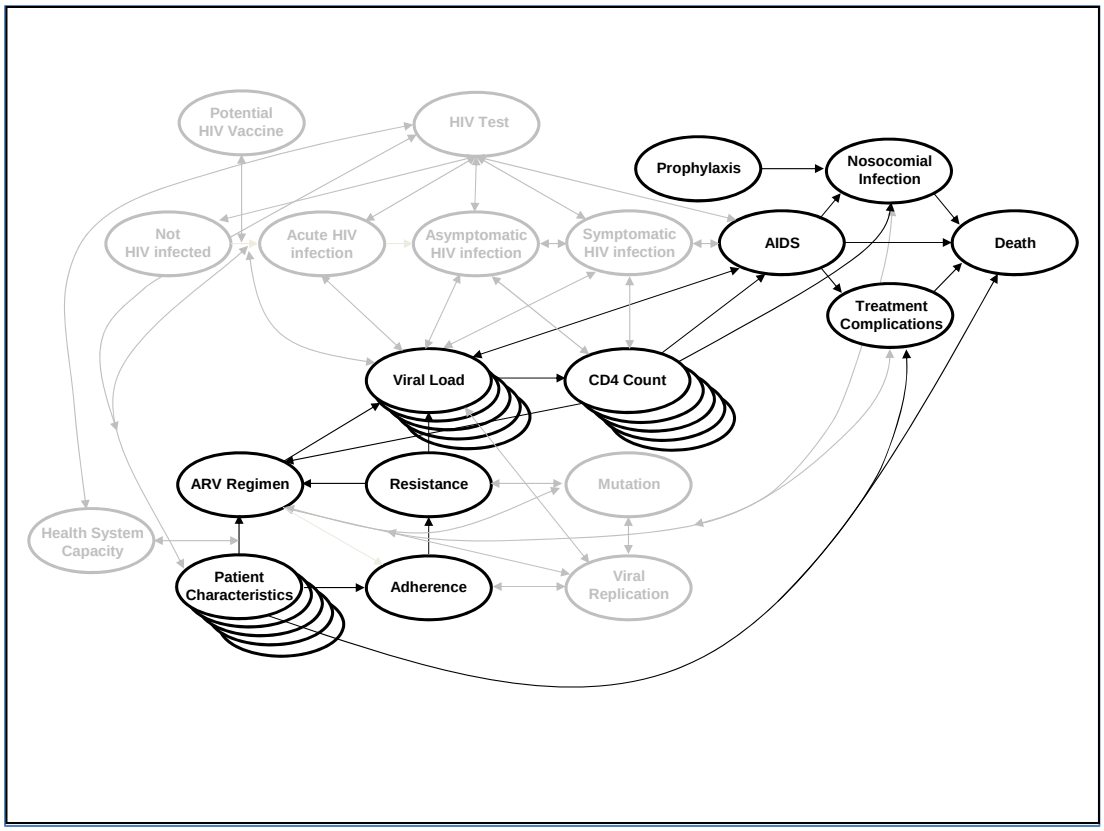

Figure A- 4 Components of the HIV conceptual model incorporated into the early individual simulation model of Freedberg, which was designed to evaluate the effect of various treatments of AIDS complications, but was later modified to include primary treatment and screening. The model characterizes patients through across many characteristics, ARV treatments, the presence of resistance, and continuous viral load and CD4 counts. The number of states required to represent all these characteristics is nearly infinite, and an individual microsimulation method was used.

Similarly, the model reported by Braithwaite (5, 6) considers many of the components already considered in the CEPAC model but in addition concentrates on the development of anti- retroviral resistance in the HIV virus, and directly models viral replication mutation and patient adherence to ART regimens (Figure A5). (7, 8)

Although similar to many cohort or microsimulation models, it does not incorporate any direct representation of infected individuals spreading the disease to uninfected individuals. As with the CEPAC model, because so many components of the disease are considered the number of states required for a standard Markov process would be prohibitive and therefore this model was also constructed as an individual Monte Carlo microsimulation.

Model using discrete event simulation (See DES modeling paper for Details)

One of the most compelling characteristics of a problem that favors the use of a DES model is the requirement of modeling interactions between individuals (the spread of infection from one individual to another or the interaction of the individuals with potentially constrained resources (a limited supply of antiretroviral doses).

One of the early representations of HIV disease as a DES model is presented in Leslie,(9) which described the difficulty of representing significant clinical detail in a dynamic transmission model.

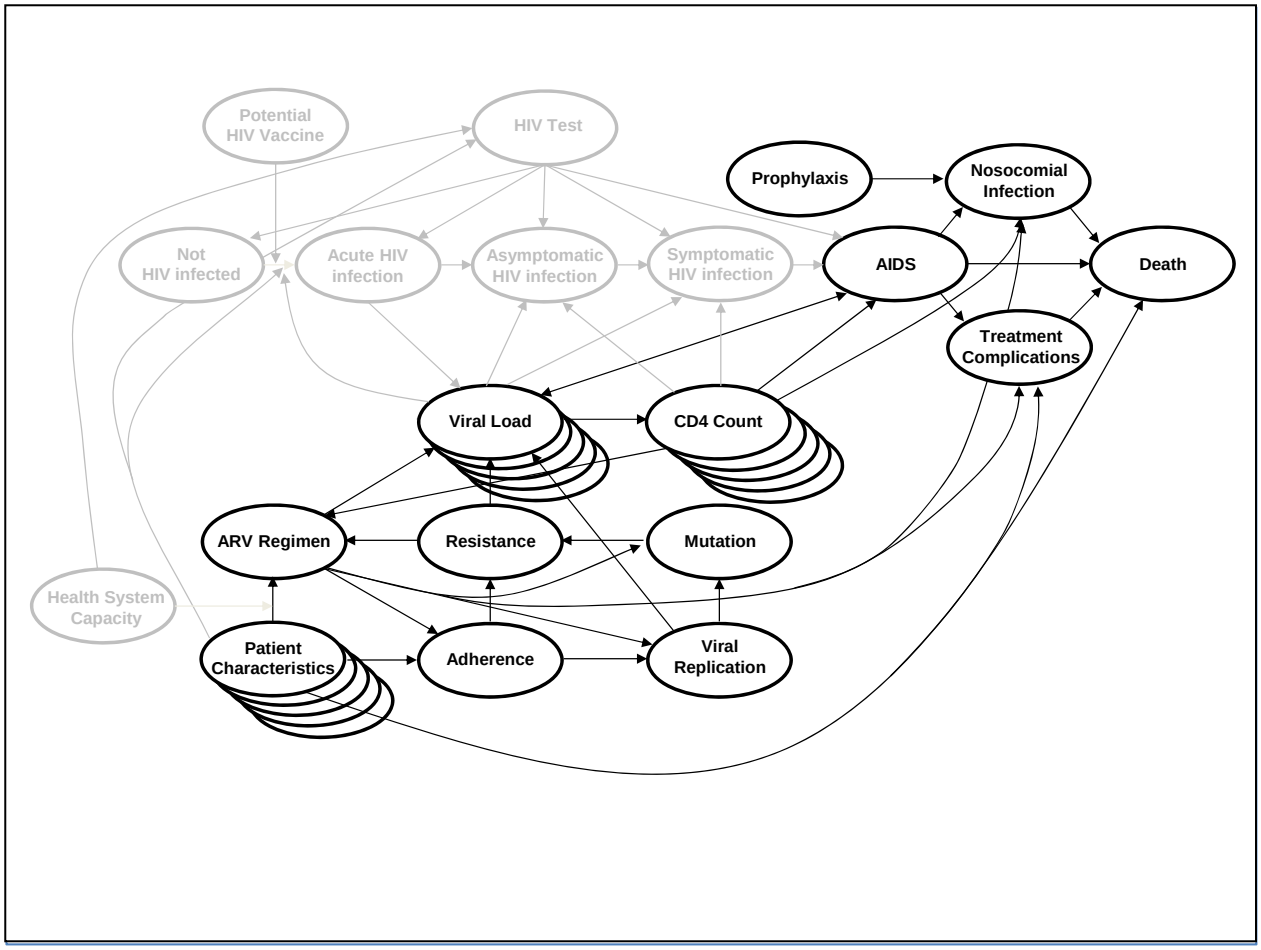

Figure A- 5 Components of the HIV conceptual model incorporated into the individual simulation model of Braithwaite, which is similar to Sanders and Freedberg in terms of characteristics and CD4 counts and viral load, and also added a biologically-based representation of the development of antiretroviral resistance. This allows for remarkably realistic representation of the development of resistance, and allows for the development of a very wide array of resistance patterns, easily represented in individual microsimulation format.

A more recent example of a standard application for DES modeling is the evaluation of different allocation strategies to treating HIV disease in the presence of resource constraints.(10)

This model was designed specifically for the purpose of predicting the clinical impact of providing limited doses of HIV therapy to patients on a first-come first serve basis compared with a strategy that allocated doses to those with lower CD4 counts. The model includes a disease progression component based on CD4 count that is mitigated by the presence or absence of treatment.

Figure A6 illustrates the basic components that this model takes into account: note that it now includes health system capacity and the limitation that places on treatment. There is no representation of the impact of these two strategies on the spread of the epidemic, nor is there significant detail regarding the development of resistance, nosocomial infections, etc. The paper finds lower morbidity and mortality in a cohort treated according to CD4 count limits as opposed to first-come first-served. This illustrates how models that allow for interaction or resource constraints can be useful and instructive even in the absence of significant clinical detail. DES models are not the only method that can incorporate constraints: resource limitations can be incorporated into dynamic transmission models as well (by limiting the flows between states). Zaric et al evaluated the impact of expanding methadone maintenance programs (which decrease HIV infection from heroin use and other risky behaviors) on the clinical and economic costs of the HIV epidemic.(11)

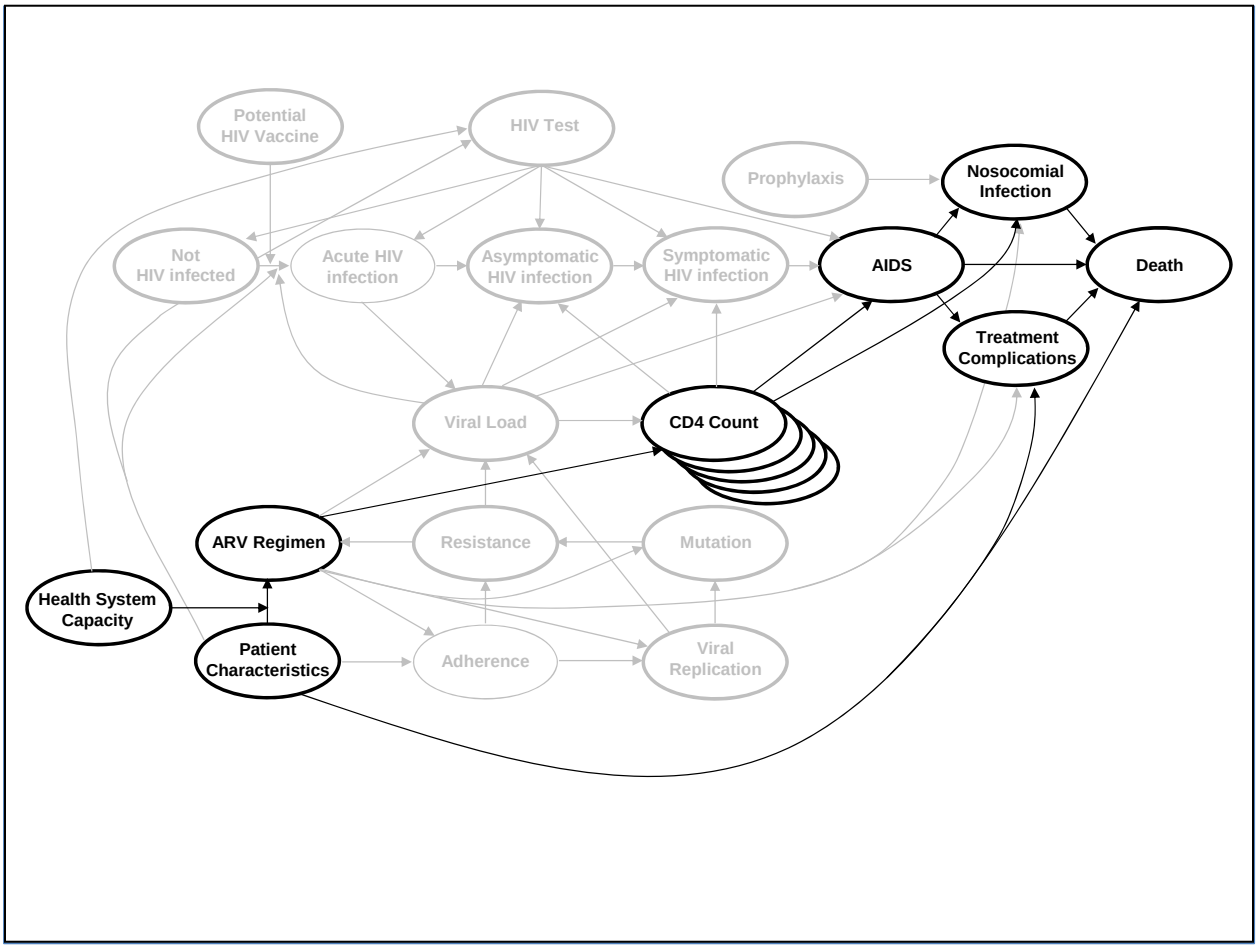

Figure A- 6 Components of the HIV conceptual model incorporated into the discrete event simulation model of Linus, which examined allocation strategies for limited doses of antiretroviral therapy. Because the model represented reasonable complexity in the natural progression of CD4 count and HIV disease, and required the ability to impose resource constraints, a DES model was used.

Model using a compartment model (See dynamic transmission model paper for details)

Compartment models have been used for many years to understand the impact of mitigation strategies on epidemics. In HIV disease, they have been used to evaluate the heterosexual spread of HIV,(12) the effectiveness of substance abuse treatment programs to decrease HIV infection,(13) even incorporating resource constraints.(11) For this example, we describe the evaluation by Long of the potential effect of an HIV vaccine on the spread of the epidemic.

Figure A7 describes the basic components included in their model. The compartments of their dynamic transmission model included many patient characteristics (age, type of sexual partner); a disease progression module that included asymptomatic infection, symptomatic infection and AIDS, progression through these states is related to CD4 count and the presence or absence of treatment. The presence of treatment in an infected individual and the presence of having had the vaccine in an uninfected individual mitigate the likelihood of transmission.

Dynamic transmission models were designed to represent the conversion of uninfected to infected individuals, and incorporate variables and characteristics that impact those transitions.

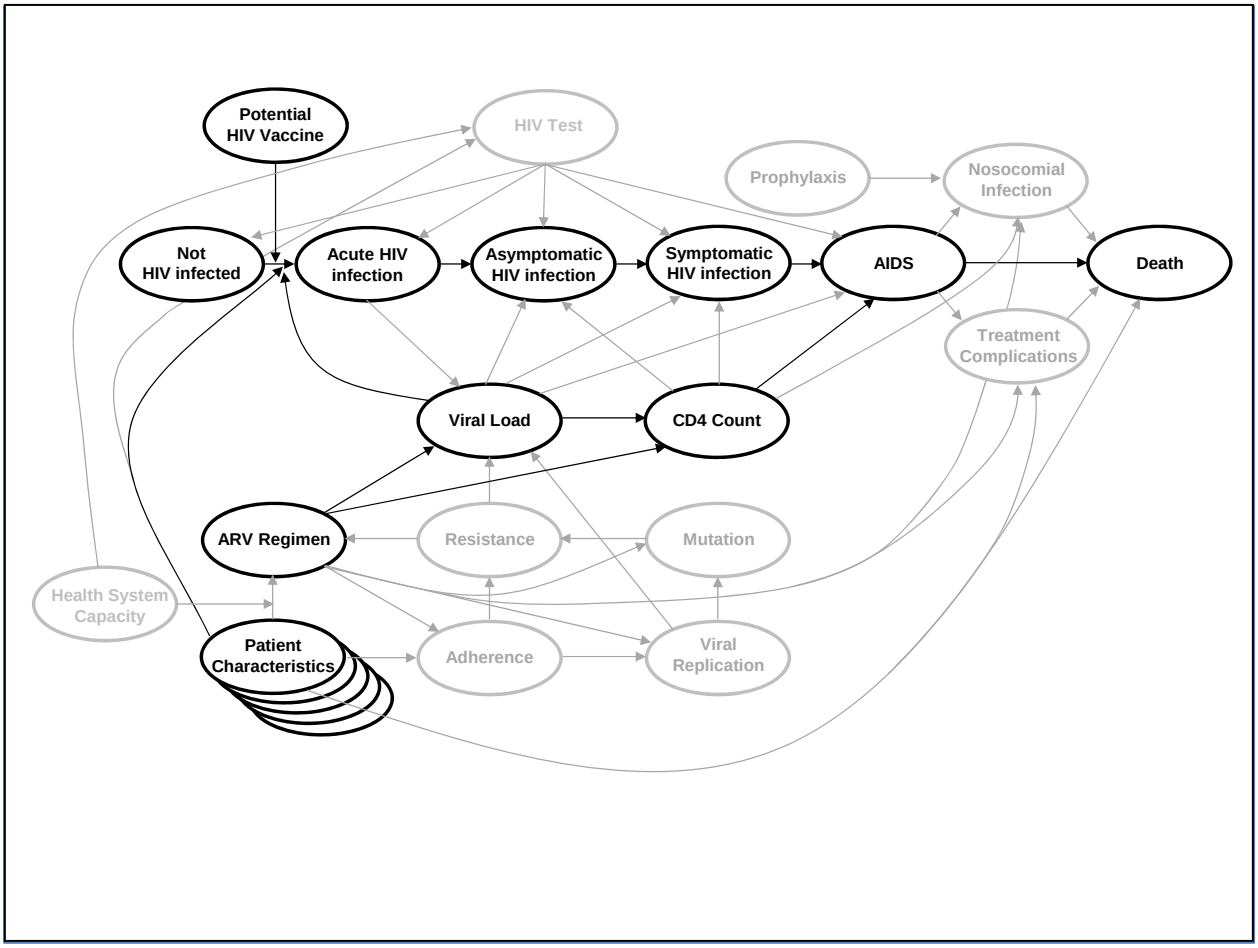

Figure A- 7 Components of the HIV conceptual model incorporated into the dynamic transition model of Long, which used a dynamic transmission model to represent the potential for a hypothetical vaccine to mitigate the transmission of HIV. The effect of the vaccine is represented by changing the rates at which uninfected persons mixing with infected persons acquire infections. The model represented 144 compartments, with differential equations representing flows between these compartments.

Summary

We have described a series of models related to problems and decisions in HIV disease for which specific modeling methods were chosen. Characteristics that determined the most appropriate modeling methods include the time horizon that is to be modeled, whether patients in the model are to be represented as individuals or groups, and whether the model must account for interactions between individuals in the model or whether the individuals in the model may be subject to constraints. These characteristics are not absolute: long time horizons may be accounted for in simple decision trees provided the effect of current decisions on future events can be represented by single global outcomes, such as the effect of the decisions on life expectancy, even though most modelers would choose a state-based transition model or a DES type model for long time horizons as they may explicitly represent the longitudinal nature of natural histories and long-term risks.

Decisions regarding whether to use cohort-based simulation or individual microsimulation are somewhat more user-dependent. As the state space expands to hundreds or thousands of potential states, it may be technically easier to represent the problem as an individual microsimulation, although there is little (if any) theoretical difference between the two. However, if the conceptualization of the problem requires that a particular variable or characteristic be in-

cluded in the representation as a continuous parameter, a modeling method that allows for each individual to be represented (state transition model simulated as an individual microsimulation, discrete event simulation or agent-based simulation) may be required.

When the problem requires the modeling of interactions between individuals, the modeling methods that incorporate this explicitly (dynamic transition models, DES and agent-based models) are the more appropriate techniques. The decision between using dynamic transition models vs. a simulation technique (DES or agent-based) is somewhat less straightforward. Our experience is that the representation of high levels of clinical complexity is much more difficult to incorporate into dynamic transition models than simulation, whereas dynamic transition models may have the ability to directly provide analytic answers and insights into the importance of particular relationships (often termed "structural properties") that may be less obvious to uncover in simulation models.

These examples are illustrative, and do not imply an absolute set of modeling requirements. However, they provide guidance from the literature regarding how the specific set of problem characteristics being modeled may favor a particular modeling method.

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