Poster #698

A Multi-State Markov Model for the Natural History of Recent, Drug-naive HIV Infection and the Initiation of Anti-Retroviral Treatment

LW Walker[1], SDW Frost[1], SJ Little[1]

[1]University of California, San Diego; San Diego, California, USA

Lorne Walker
University of California – San Diego
Dept. of Biomedical Sciences
Ph: 619.543.4774
Fax: 619.543.5094
lwwalker@ucsd.edu

Abstract

HIV infection and clinical antiretroviral (ARV) treatment represent a complex system of biology and clinical medicine that influence disease outcome in patients. We proposed to develop a multi-state Markov model to describe the events of early HIV-infection and treatment initiation in recently-infected, drug-naive HIV+ patients. In a retrospective analysis, we identified a cohort of 194 patients from a primary infection study who remained drug-naive for a minimum of 120 days beyond the estimated date of infection. ARV-naive patients were considered to be in one of four clinical states defined as "high" or "low" VL and CD4 using thresholds of 100,000 copies/ mm^3 and 350 cells/ mm^3 respectively. A fifth state represents the initiation of ARV treatment, and is the endpoint for this analysis. A transition rate matrix describing movement from state-to-state was defined by maximum likelihood (ML) methods for baseline data as well as in conjunction with covariates to elucidate factors that influence the natural history of HIV infection. This model converged to a ML estimate with estimated 95% confidence intervals. Some covariates produced statistically significant changes in transition probability, including the presence of Acute Retroviral Syndrome (ARS) symptoms, some HLA alleles, and the estimated date of infection.

Methods

Patients (N=194) were selected from a clinical database of primarily-infected patients. Patients were included in analysis if they remained drug-naive for a minimum of 120 days beyond the estimated date of infection (EDI), and had one or more measurement of both VL and CD4 beyond 120 days post-EDI. The first 120 days post-infection were discarded to allow patients to reach their viral set-point, after the acute phase of infection passed. Patients were classified into one of five states as outlined in figure 1. States 1-4 include drug naive patients classified by VL and CD4 using thresholds of 100,000 copies/ mm^3 and 350 cells/ mm^3. State 1 included patients with low VL and high CD4, state 2 patients with high VL and high CD4, state 3 low VL and low CD4, and finally, state 4 patients with high VL and low CD4. State 5 was an absorbing state, included patients who initiated ARV therapy, and is the endpoint for this analysis. It was assumed that patients could move between any two states (except state 5), and a maximum likelihood method was used to estimate the transition rate matrix describing the probability of moving between states. State transitions were filtered to ensure that only clinically-significant changes in clinical measurements were recognized as valid transitions. To validate a change between "high" and "low" CD4, either two consecutive measurements of CD4 above or below threshold, or a measurement > 50 cells/mm3 from threshold values were required. A two-fold change in VL from the last-observed value in the previous state was required to validate transitions in viral load. Effects of covariates on transition intensities were assessed by a proportional hazards model. Covariates examined included age, first state occupied, EDI, co-infection with other STI's, Center for Epidemiological Study (CES) depression scores, presence of ARS symptoms, HLA genotype and pol polymorphisms. All analysis was conducted using the R programming language and msm package.

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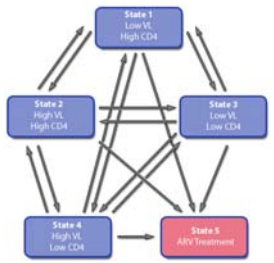
Figure 1



Multi-State Markov Model

Table 1:

From: \ To:	1	2	3	4	5
1	1145	22	39	0	57
2	37	256	1	18	23
3	17	0	117	2	28
4	0	3	5	34	12

Transitions Observed in ARV-naive cohort

Table 2

Demographic Information (mean [range])

Age	33 [19-57]	**Gender**	Male: 189 (97%) Female 5 (3%)
EDI	2/25/03 [7/24/96-2/16/07]	**Time to therapy (years)**	1.4 [0.38-5.4]
VL	4.91 log10 copies/ml [1.14-6.99]	**CD4**	541 cells/ml [61-1639]

Table 3:

From: \ To:	1	2	3	4	5
1	0.55	0.076	0.066	0.019	0.29
2	0.43	0.073	0.071	0.026	0.40
3	0.21	0.028	0.13	0.021	0.61
4	0.17	0.03	0.11	0.032	0.65

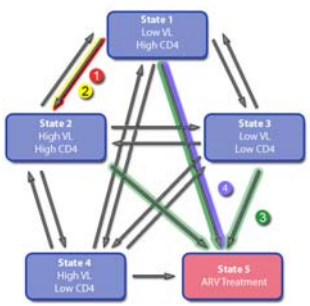
1 Year Transition Probability Matrix

Table 4:

From: \ To:	1	2	3	4
1	0.77	0.11	0.093	0.026
2	0.72	0.12	0.12	0.043
3	0.54	0.072	0.33	0.054
4	0.50	0.088	0.32	0.94

1 Year Transition Probability Matrix- ARV naive only

Figure 2:



Covariate Effects on Transition Probabilities:

1. Acute Retroviral Syndrome Symptoms
   1→2 HR: 8.6 [2.0-36.0]
2. C4 HLA Allele
   1→2 HR: 3.5 [1.7-7.2]
3. Estimated Date of Infection
   1→5 HR: 0.71 [0.55-0.92]
   2→5 HR: 1.61 [1.00-2.58]
   3→5 HR: 1.52 [1.1-2.1]
4. Time Since Infection
   1→5 HR: 0.51 [0.33-0.79]

Results

Analysis of this Markov model yielded ML estimates of the transition rate matrix for this cohort in conjunction with each covariate. Where possible, a 95% confidence interval was also estimated. This transition matrix can be used to calculate the probability of a patient moving between states over time. This is summarized in tables 3 and 4. Patients with high VL and/or low CD4 were significantly more likely to begin treatment than those with in state 1 (Ratio(2→5/1→5): 2.5 [1.2-5.3], ratio(3→5/1→5): 5.3 [3.1-9.2], ratio(4→5/1→5): 6.4 [2.7-15.2]). Some covariates demonstrated significant effects on the transition probability matrix. The probability of transition from state 1 to state 2, reflecting an increased VL without concurrent CD4 decline, by the reporting of ARS symptoms (HR: 8.6, 95% CI [2.0-36.0]), and possessing one or more C4 HLA alleles (HR: 3.5, [1.7-7.2]). The effect of estimated date of infection (EDI) on transition rates into state 5 demonstrate a changes in the initiation of ARV therapy over time (1→5 HR: 0.71 [0.55-0.92], 2→5 HR: 1.61 [1.00-2.58], 3→5 HR: 1.52 [1.1-2.1]). Covariates that were analyzed but did not yield significant results include other HLA alleles, co-infection with other STIs, drug use and sexual behavior questionnaire responses, and pol sequence polymorphisms. Only the transition 1→5 was effected by the number of days since infection (HR: 0.51 [0.33-0.79]), suggesting that transition probabilities were not time dependent for a given subject. These findings are summarized in tables 3 and 4, and figure 2

Conclusions

This Multi-State Markov Model describes HIV disease in drug-naive patients.

- **This Multi-State Markov Model describes the natural history of HIV in drug-naive patients**
  - Patients in state 1 (low VL, high CD4) who do not begin ARV therapy have a 77% probability of demonstrating no disease progression after 1 year.
  - Patients in state 2 (high VL) or state 3 (low CD4) who do not begin ARV therapy are more likely to revert to state 1 than progress to or remain in more advanced states .
- **This Multi-State Markov Model describes the clinical decision to initiate ARV therapy**
  - Patients in less favorable states (2,3,4) are more likely to initiate ARV therapy than those in state 1 .
  - Recently enrolled patients are more likely to initiate ARV therapy later in disease course (from states 2 or 3) and less likely to initiate ARV therapy from state 1.
  - The longer patients wait to initiate ARV therapy, the less likely they are to be in state 1 when treatment initiated (transition directly from 1→5).
- **This Multi-State Markov Model describes factors that change the ways HIV progresses**
  - Patients who possess the C4 HLA allele have a higher probability of moving from state 1 to state 2 (developing high VL)
  - Patients who experienced Acute Retroviral Syndrome symptoms have a higher probability of moving from state 1 to state 2 (developing high VL)

Summary & Future Directions

Some features of the described model reinforce previously known features of the disease system:

- The C4 HLA allele is known to be unfavorable in HIV infection
- ARV treatment standards have changed over time, supporting dependence of transition probabilities on EDI

Other features are not well described elsewhere:

- Presence of ARS symptoms predict a higher probability of developing high VL

This analysis may be limited by lacking observations on some possible transitions (ex: 4 → 1, 2 → 3), and incomplete data for some individuals and covariates. A bayesian approach to this model may prove more robust.