

A Markov Cure Model To Compare Progression Of HIV-1 And HIV-2 Infection

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Some facts on HIV and AIDS

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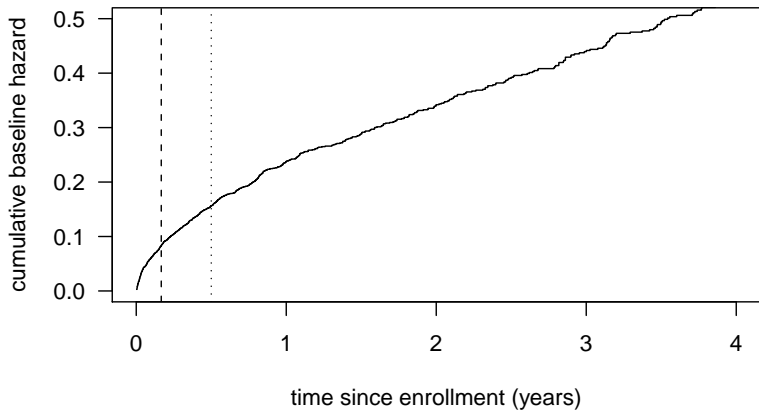
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 - **HIV-2**: mainly in West Africa
Observed: slower decline in CD4 T-cells, lower mortality

Aim and Data

- **Aim**
 - Estimate fraction of non-progressors among HIV-2 (and HIV-1)
 - Compare progression of HIV-1 and HIV-2 infected individuals

Cumulative baseline hazard, Cox with time-updated CD4



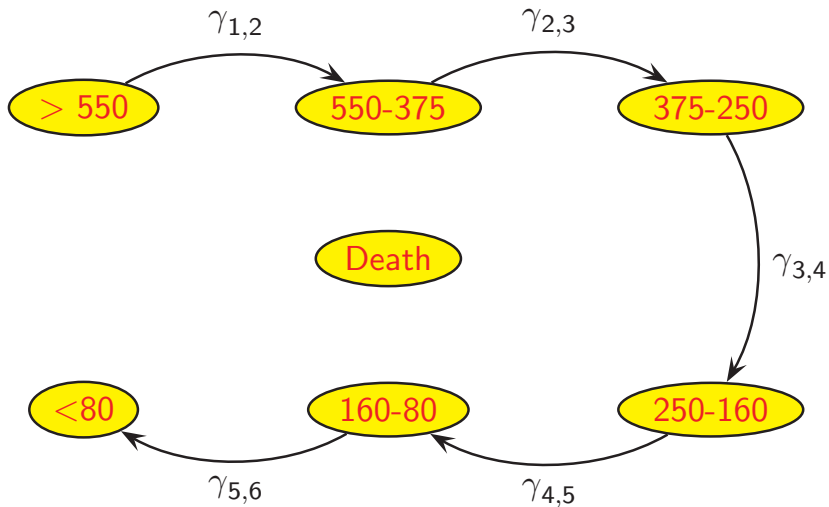
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 - Tested: Individuals with STI, HIV-related symptoms, female commercial sex worker and others \implies advanced progressors overrepresented \implies **exclude first 2 months**

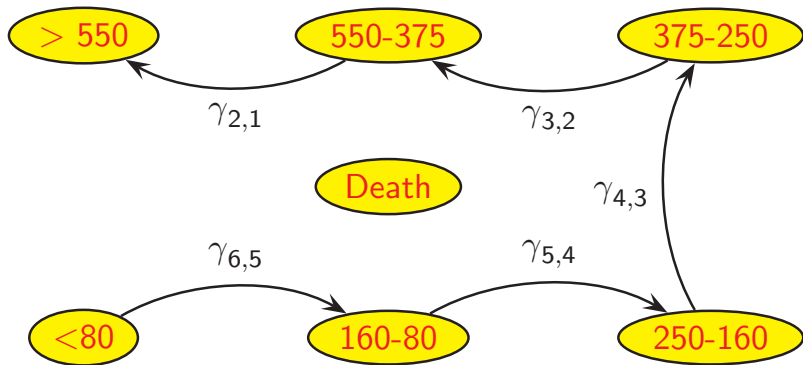
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 - CD4 T-cell count every six months
 - Intensive follow-up, cause of death largely unknown
 - HIV+ included, date of HIV infection mostly unknown \implies Markov model

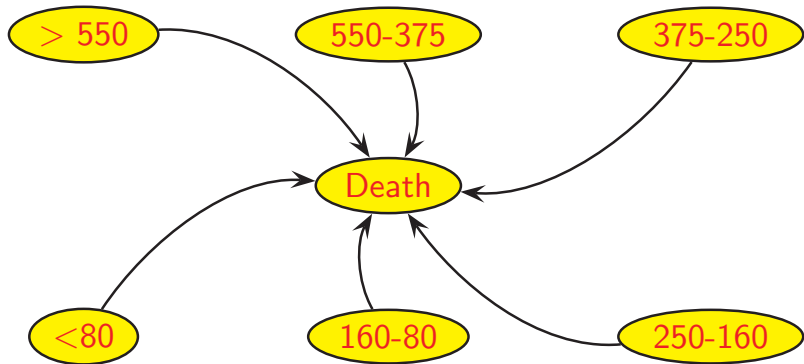
Forward transitions



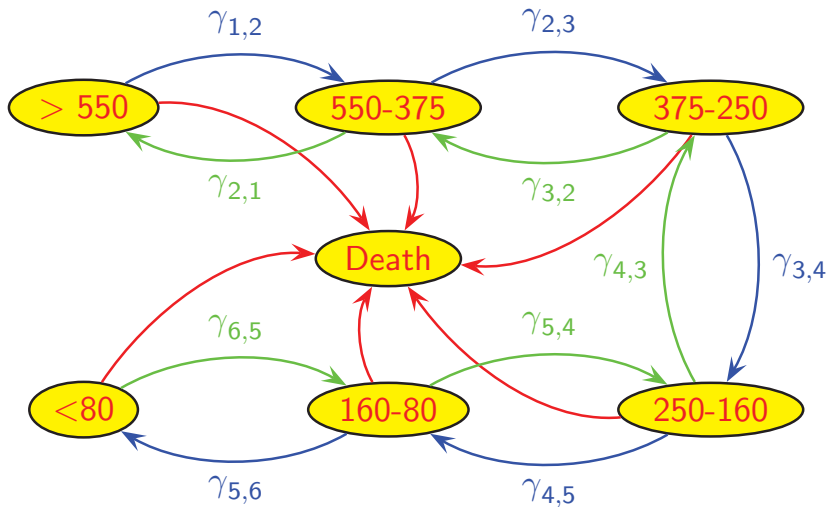
Backward transitions



Transitions to death



All together



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- Likelihood data with non-progression

$$P(\text{data}) = P(\text{data}|\text{non-progressor}) \times (1 - P(\text{progressor})) \\ + P(\text{data}|\text{progressor}) \times P(\text{progressor})$$

with

non-progressor : latent state (may depend on sex and age)

data|non-progressor : stable and high CD4 count; death risk is small

data|progressor : lower and decreasing CD4 count;

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- Two stages:
 1. smooth CD4 pattern and determine progression status
 2. Markov model for progressors

Model: part 1

- Model CD4 via random effects model

$$\text{CD4}^{1/3}(t_{ij}) = a_i + b_i \times t_{ij} + \varepsilon_{ij}$$

with $(a_i, b_i) \sim N((\mu_1, \mu_2), \Sigma)$

μ_1 and μ_2 depend on sex and age

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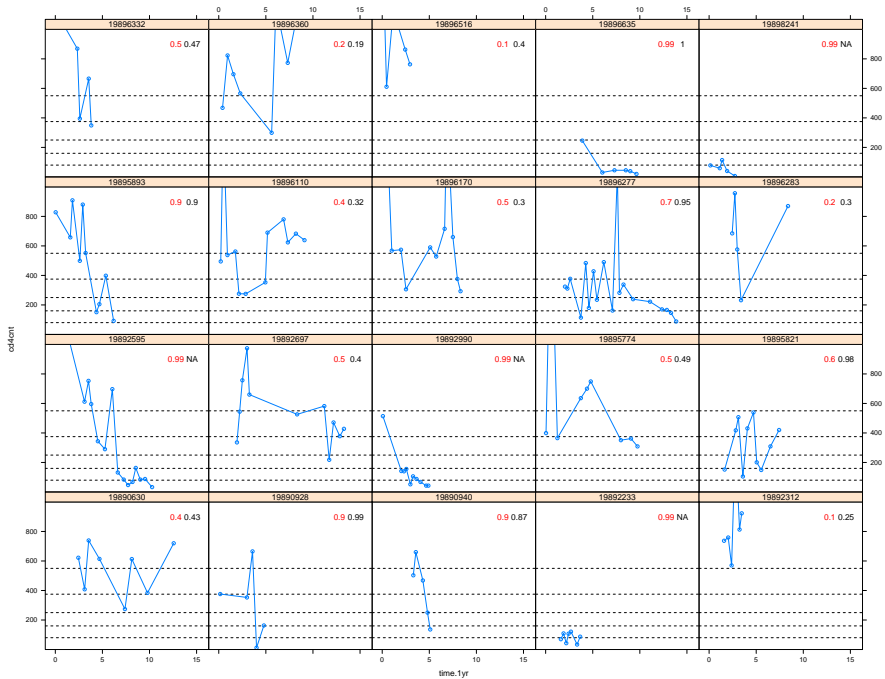
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- Non-progressors: $\mu_2 = 0$
- sure progressors: last CD4 < 375 before death within 1 year or RNA > 10,000

```
cd4[i] ~ dnorm( modelcd4[i], tau.eps);
modelcd4[i] <- latentcd4[i, T[person[i]]];
latentcd4[i, 1] <- RE.cure[person[i], 1] + RE.cure[person[i], 2]*time[i];
latentcd4[i, 2] <- RE.prog[person[i], 1] + RE.prog[person[i], 2]*time[i];
```

$T[\text{person}[i]] \sim \text{dbern}(p.\text{prog})$ changes per iteration





Model: part 2, Markov

- Calculate states based on fitted values, no feedback

```
if(T[person[i]] = 2)
  cd4.cat[i] <- cat(latentcd4[i,2]);
state[i] <- cut(cd4.cat[i]);
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- Assume constant transition rates
- Only progressors used in Markov model

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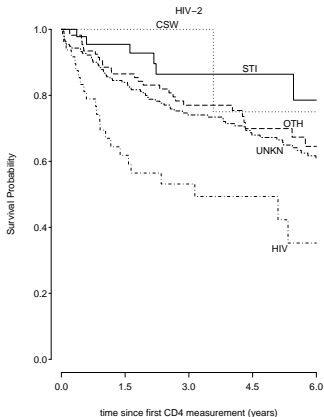
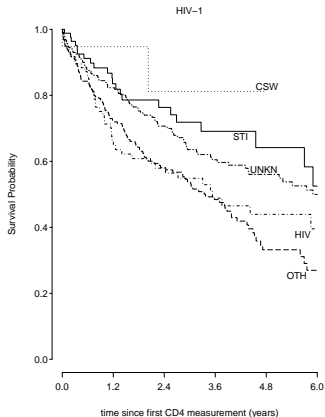
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- Use WinBUGS differential interface WBDiff solving $P(t)' = P(t)G$
Matrix exponential: $P(t) = \exp(Gt)$

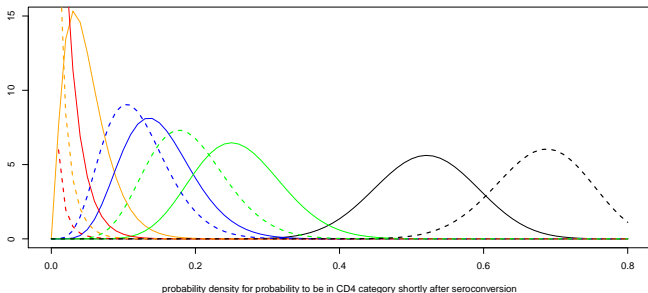
Results: Progression Probability

In cohort: HIV-2: $P(\text{prog}) = 71\%$; HIV-1: $P(\text{prog}) = 98.7\%$



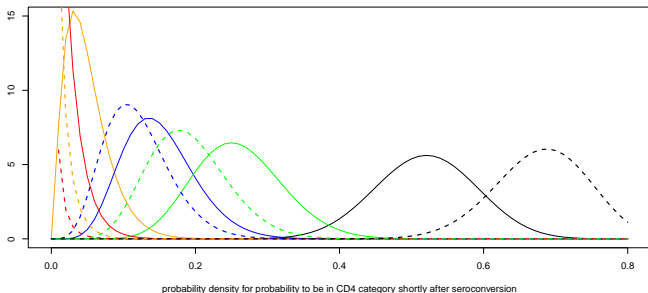
Progression Probability in Population

- Assume Dirichlet distribution of CD4 count shortly after HIV seroconversion



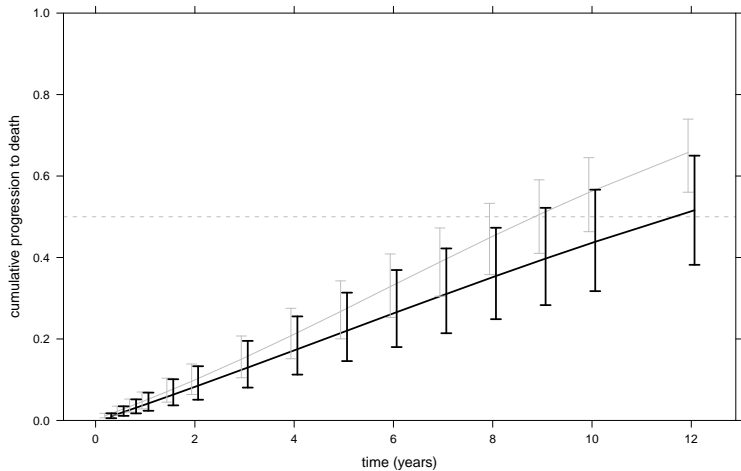
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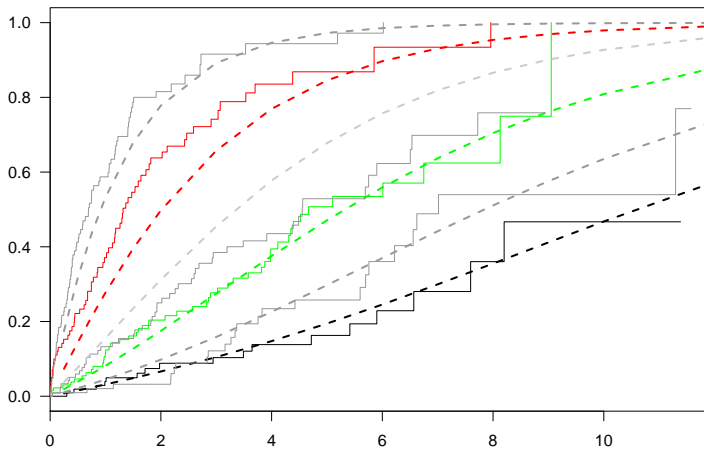


- HIV-2: $P(\text{prog}) = 54\%$ (95% CI 41% to 67%)
HIV-1: $P(\text{prog}) = 98.5\%$ (95% CI 93.9% to 100%)

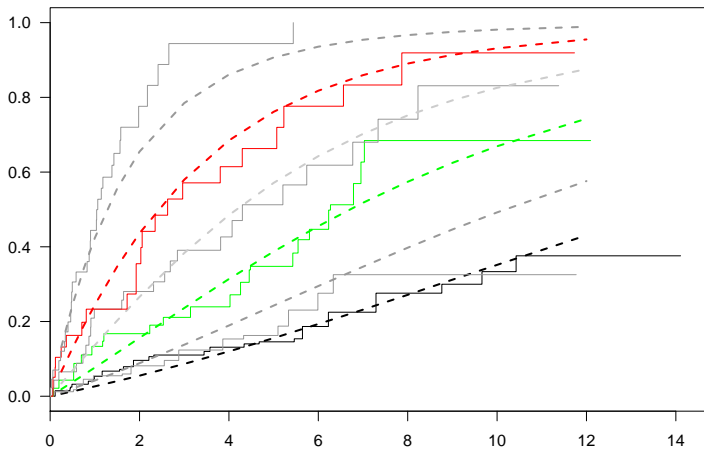
Progression from HIV seroconversion to death



Comparison with crude Kaplan-Meier, HIV-1



Comparison with crude Kaplan-Meier, HIV-2



Remarks

- Using marker information helps in classifying non-progressors
- Markov model to model time to event distribution if time origin is mostly unknown
- Bayesian analysis best way to take into account all uncertainty

