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

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Some facts on HIV and AIDS

- HIV virus multiplies in helper T lymphocytes (CD4 T-cells) \[\Rightarrow\]
  CD4 cells decrease after infection \[\Rightarrow\] AIDS \[\Rightarrow\] death

- Two main types
  - HIV-1: pandemic, typical course (before treatment): infection \[\leq\] 0.5 yr \[\rightarrow\] seroconversion: HIV- to HIV+ 10 yrs \[\rightarrow\] AIDS 2 yr \[\rightarrow\] death
  - Most results based on cohort studies in developed world
  - HIV-2: mainly in West Africa
    - Observed: slower decline in CD4 T-cells, lower mortality
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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

- **Data**
  - Tested: Individuals with STI, HIV-related symptoms, female commercial sex worker and others
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Cumulative baseline hazard, Cox with time-updated CD4
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• Data
  • Tested: Individuals with STI, HIV-related symptoms, female commercial sex worker and others → advanced progressors overrepresented → exclude first 2 months
  • CD4 T-cell count every six months
  • Intensive follow-up, cause of death largely unknown
  • HIV+ included, date of HIV infection mostly unknown → Markov model
Forward transitions

\[ \gamma_{1,2}, \gamma_{2,3} \]

\[ > 550 \rightarrow 550-375 \rightarrow 375-250 \rightarrow 250-160 \rightarrow 160-80 \rightarrow <80 \rightarrow > 550 \]

\[ \gamma_{3,4}, \gamma_{4,5}, \gamma_{5,6} \]
Backward transitions

\[
\begin{align*}
& > 550 \
\quad \rightarrow & 550-375 \
& \gamma_{2,1} \
\quad \rightarrow & 375-250 \
& \gamma_{3,2} \
\quad \rightarrow & \text{Death} \
& \gamma_{4,3} \
\quad \rightarrow & <80 \
& \gamma_{6,5} \
\quad \rightarrow & 160-80 \
& \gamma_{5,4} \
\quad \rightarrow & 250-160
\end{align*}
\]
Transitions to death

- > 550
- 550-375
- 375-250
- <80
- 160-80
- 250-160
All together

> 550 -\(\gamma_{1,2}\) - 550-375

550-375 -\(\gamma_{2,1}\) - Death

Death -\(\gamma_{2,3}\) - 375-250

375-250 -\(\gamma_{3,2}\) - <80

<80 -\(\gamma_{6,5}\) - 160-80

160-80 -\(\gamma_{5,6}\) - > 550

> 550 -\(\gamma_{5,4}\) - 250-160

250-160 -\(\gamma_{4,5}\) - 375-250

375-250 -\(\gamma_{3,4}\) - > 550
Estimation

- MCMC/WinBUGS

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

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; progression described via Markov model

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

- MCMC/WinBUGS
- Likelihood data with non-progression

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Model: part 1

- Model CD4 via random effects model

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

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

\(\mu_1\) and \(\mu_2\) depend on sex and age

- Non-progressors: \(\mu_2 = 0\)
Model: part 1

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- sure progressors: last CD4 < 375 before death within 1 year or RNA > 10,000

\[
\begin{align*}
\text{cd4}[i] & \sim \text{dnorm( modelcd4}[i], \tau.\text{eps});} \\
\text{modelcd4}[i] & \leftarrow \text{latentcd4}[i, \text{T[person}[i]]);} \\
\text{latentcd4}[i,1] & \leftarrow \text{RE.cure}[\text{person}[i],1] + \text{RE.cure}[\text{person}[i],2]*\text{time}[i];} \\
\text{latentcd4}[i,2] & \leftarrow \text{RE.prog}[\text{person}[i],1] + \text{RE.prog}[\text{person}[i],2]*\text{time}[i];
\end{align*}
\]

\(\text{T[person}[i]] \sim \text{dbern(p.prog) changes per iteration}\)
Model: part 2, Markov

- Calculate states based on fitted values, no feedback
  
  ```r
  if(T[person[i]] == 2)
    cd4.cat[i] <- cat(latentcd4[i,2]);
  state[i] <- cut(cd4.cat[i]);
  ```
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- Interval censored transitions
- Assume constant transition rates
- Only progressors used in Markov model
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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

\[ P(\text{prog}) = \begin{cases} 54\% & (95\% \text{ CI } 41\% \text{ to } 67\%) \\ 98.5\% & (95\% \text{ CI } 93.9\% \text{ to } 100\%) \end{cases} \]
Progression Probability in Population

- Assume Dirichlet distribution of CD4 count shortly after HIV seroconversion

- 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

Cumulative progression to death over time (years).
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
THANKS!