# Competing risks, when and how to incorporate them in the analysis

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# Where I work

- Head of biostatistics group at OUCRU
  (Oxford University Clinical Research Unit)
  with units in Vietnam, Nepal and Indonesia
- Established in 1991 in Ho Chi Minh City, connected to Hospital for Tropical Diseases, founded in 1862

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  (Oxford University Clinical Research Unit)
  with units in Vietnam, Nepal and Indonesia
- Established in 1991 in Ho Chi Minh City, connected to Hospital for Tropical Diseases, founded in 1862
- Research institute on infectious diseases
  - Malaria: $<$10/3000 deaths per year in Vietnam/Indonesia
  - Tuberculosis: 17,000/100,000 deaths per year in Vietnam/Indonesia
  - Dengue: $<$50/500 deaths in Vietnam/Indonesia
  - Tetanus, Diphteria, Measles, Hand Foot Mouth Disease, ...
  - Drug resistant infections: $>$40,000/$>$100,000 deaths per year in Vietnam/Indonesia

# Outline

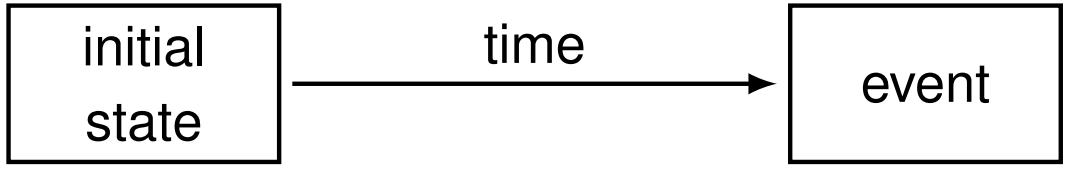
**Competing Risks; When**

Competing Risks; How

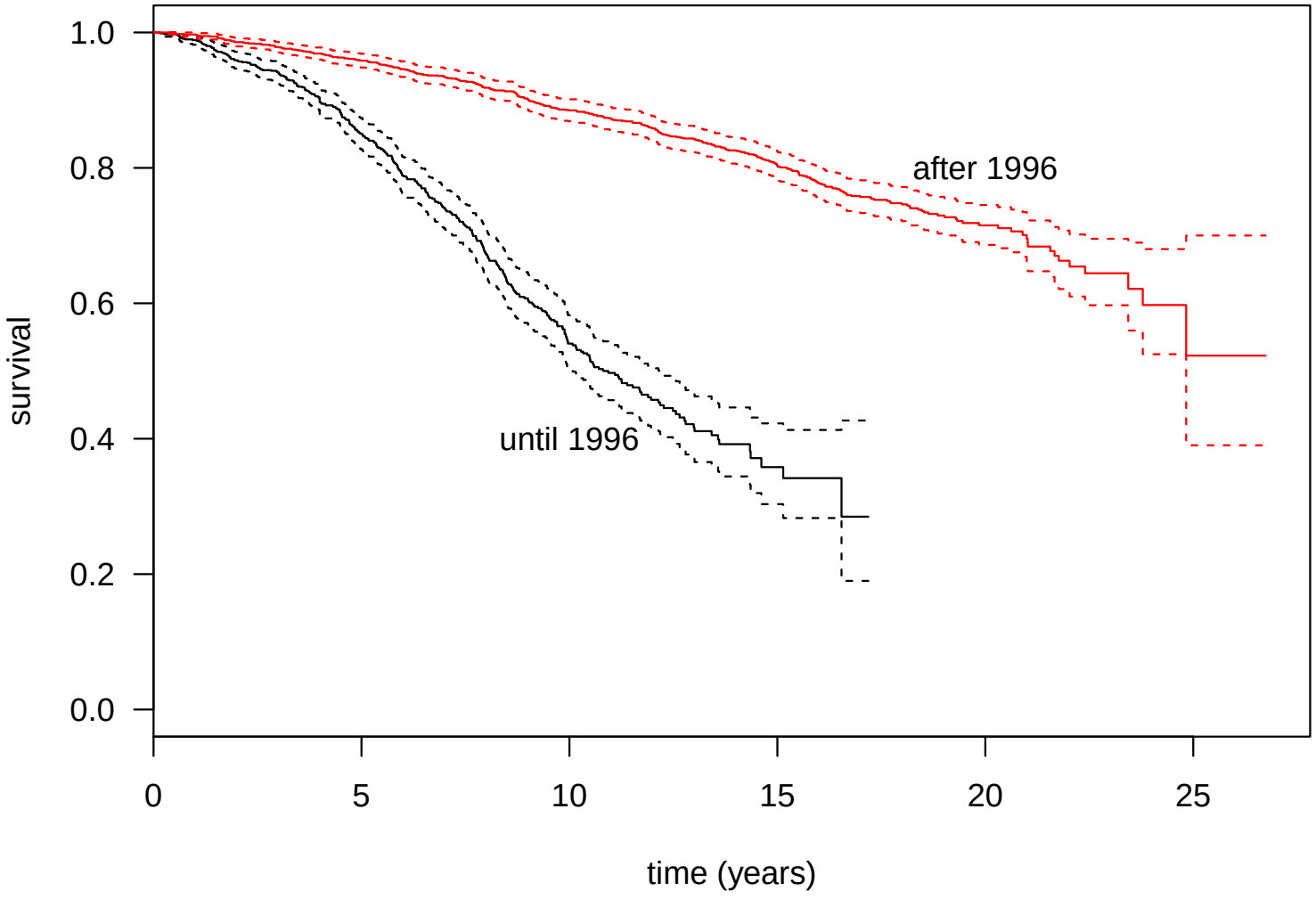
Which Approach to Choose?

# Beyond classical survival analysis

- Classical: transition between two states, one event type.
  "We all die, but not all at the same age"



# Example: death after HIV infection, powerful therapy since 1996




Problem: right censored data $\longrightarrow$ rate/hazard

## Rate and Risk

$T$ time to event (e.g. death)

- Risk: $\mathrm{P}(T \leq t)$ (or survival $\mathrm{P}(T > t)$)
- Rate (hazard, incidence):

$$\lambda(t_l) = \mathrm{P}(T = t_l \,|\, T \geq t_l) \qquad \textit{discrete}$$

$$\lambda(t) = \lim_{\Delta t \downarrow 0} \frac{\mathrm{P}(t \leq T < t + \Delta t \,|\, T \geq t)}{\Delta t} \qquad \textit{continuous}$$

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- Hazard basis for
  - Kaplan-Meier

# Kaplan-Meier

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|---|---|---|---|---|---|---|---|---|
| death | 1 | 2 | 6 | 11 | 9 | 11 | 2 | 60 |
| censor | 5 | 9 | 6 | 6 | 9 | 12 | 4 | 86 |

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$$\begin{aligned}\mathrm{P}(>\text{6 year alive}) = &\mathrm{P}(\text{ year 0-1 alive})\times \\ &\mathrm{P}(\text{ year 1-2 alive} \mid \text{alive until year 1})\times \\ &\ldots\times \\ &\mathrm{P}(\text{ year 5-6 alive} \mid \text{alive until year 5}) \\ &= (1-h_{0\text{-}1})\times(1-h_{1\text{-}2})\times(1-h_{2\text{-}3})\times\ldots\times(1-h_{5\text{-}6})\end{aligned}$$

Assumption: censored individuals represented by those at risk

Year 0-1: $h_{0\text{-}1} = 1/146 = 0.006849$

Year 1-2: $h_{1\text{-}2} = 2/140 = 0.014286$

Year 2-3: $h_{2\text{-}3} = 6/129 = 0.046512$ etc.

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- Hazard basis for
  - Kaplan-Meier
  - Cox model $\lambda(t) = \lambda_0(t) \exp\{\beta_1 X_1 + \ldots + \beta_p X_p\}$

# Beyond classical survival analysis

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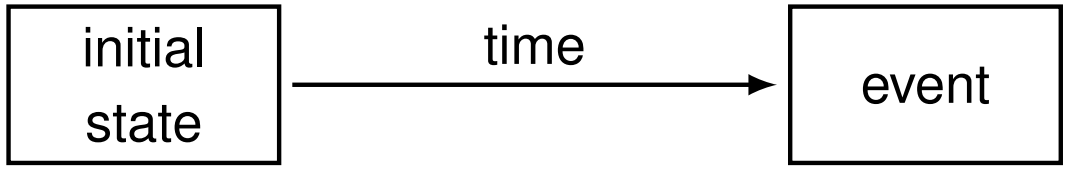
  "We all die, but not all at the same age"




- Life and death are richer than that
  1. Multiple causes of death. Competing risks:
     Event-type outcomes that are mutually exclusive
     "we all die, but not all at the same age and from the same cause"

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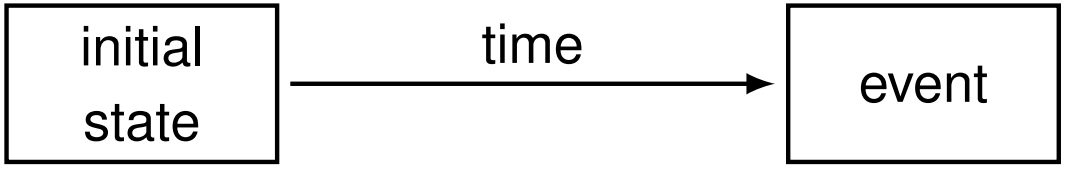


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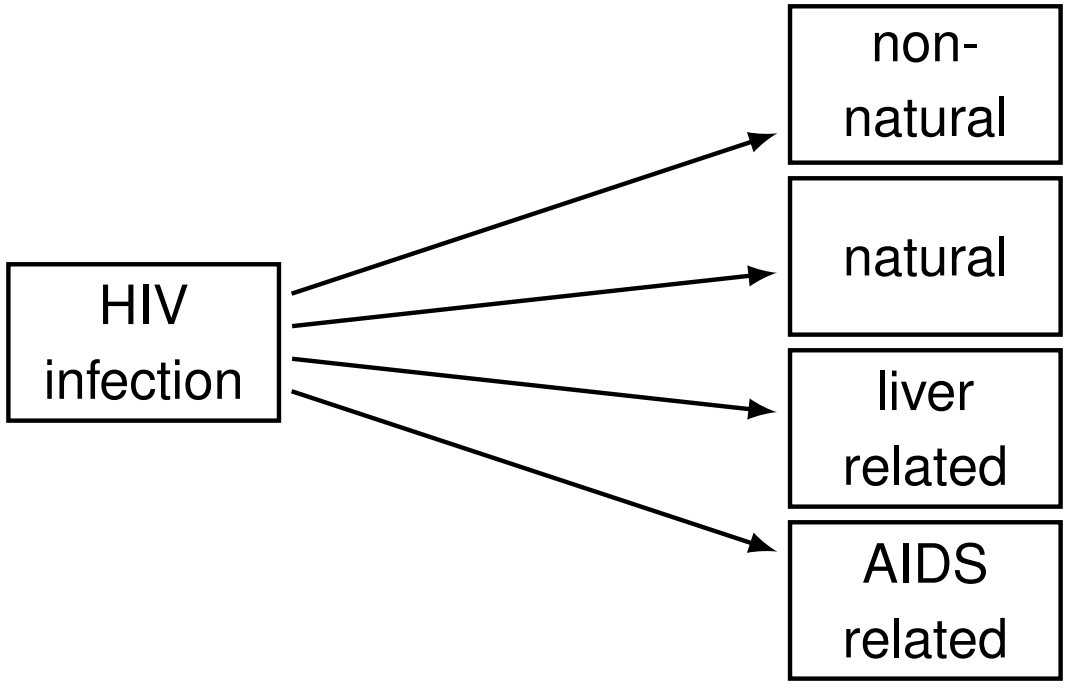
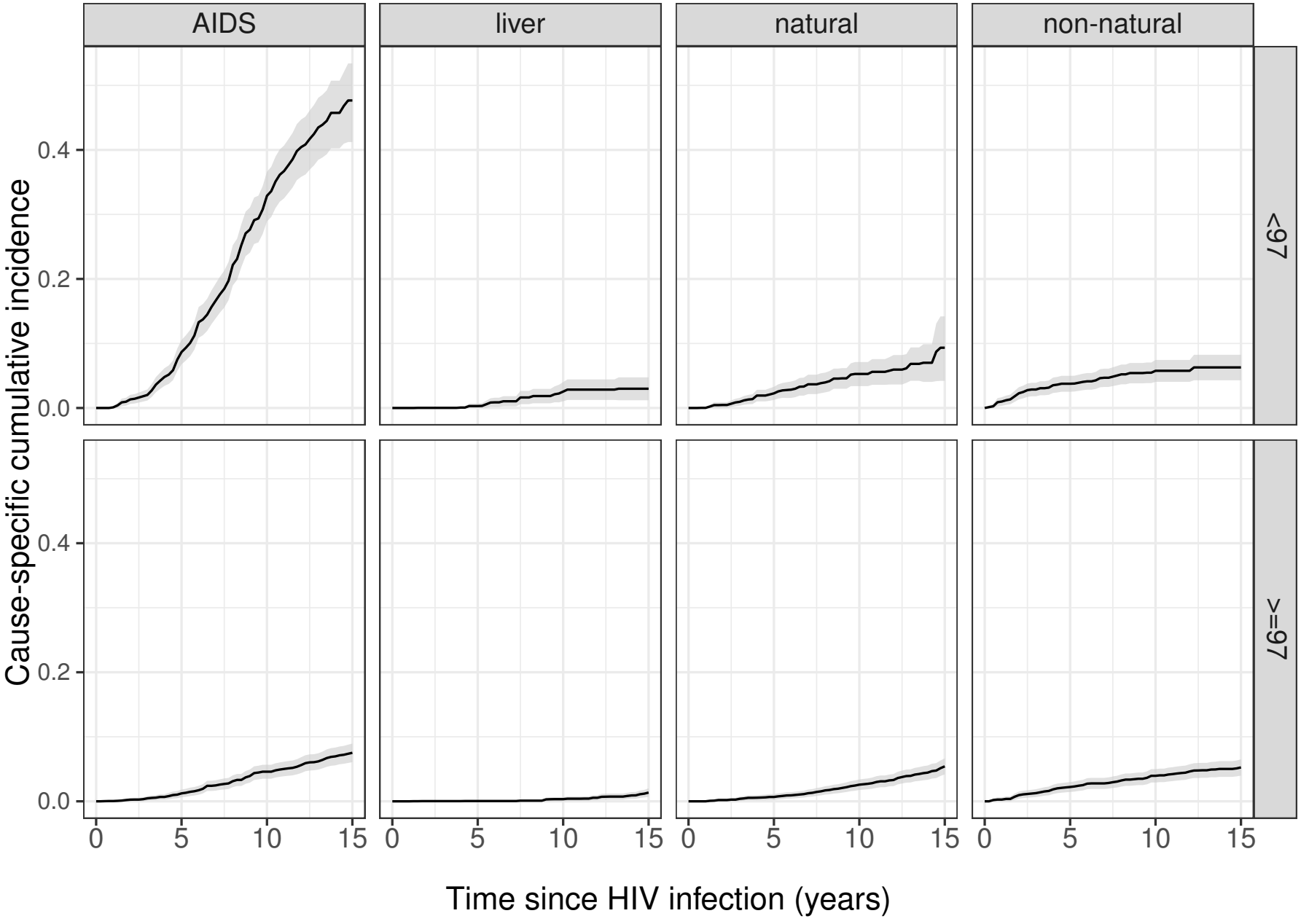
# I: Causes of death (COD) after HIV infection




- Has the spectrum in causes of death changed after the introduction of cART (combination anti-retroviral therapy)

# Cause-specific mortality by calendar period



# Role of competing risks

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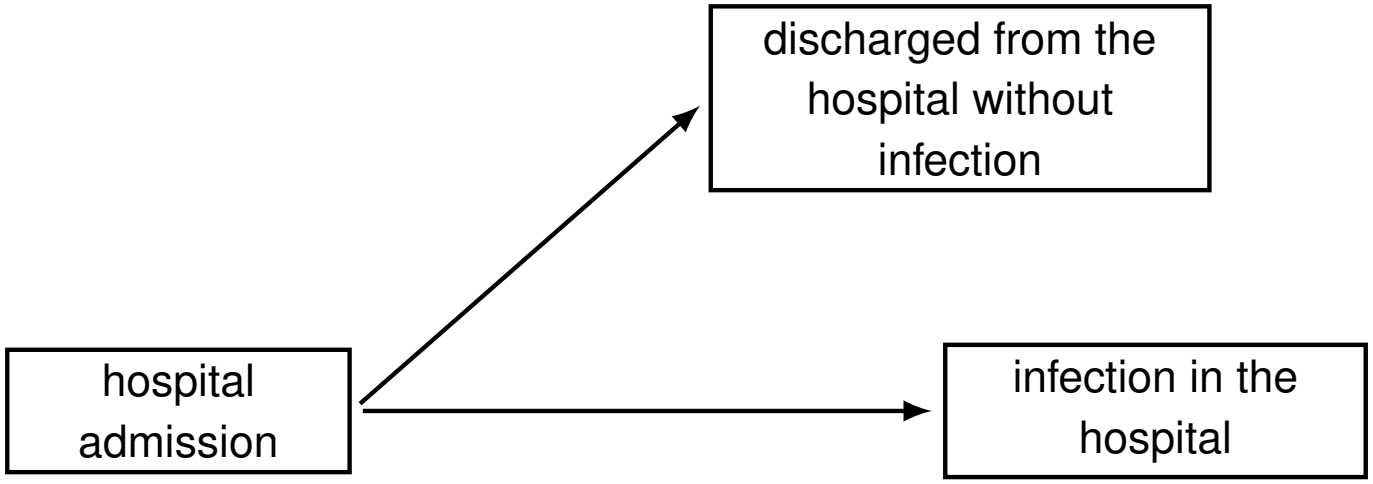

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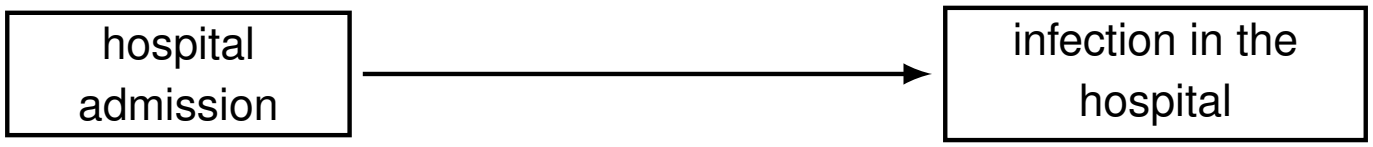


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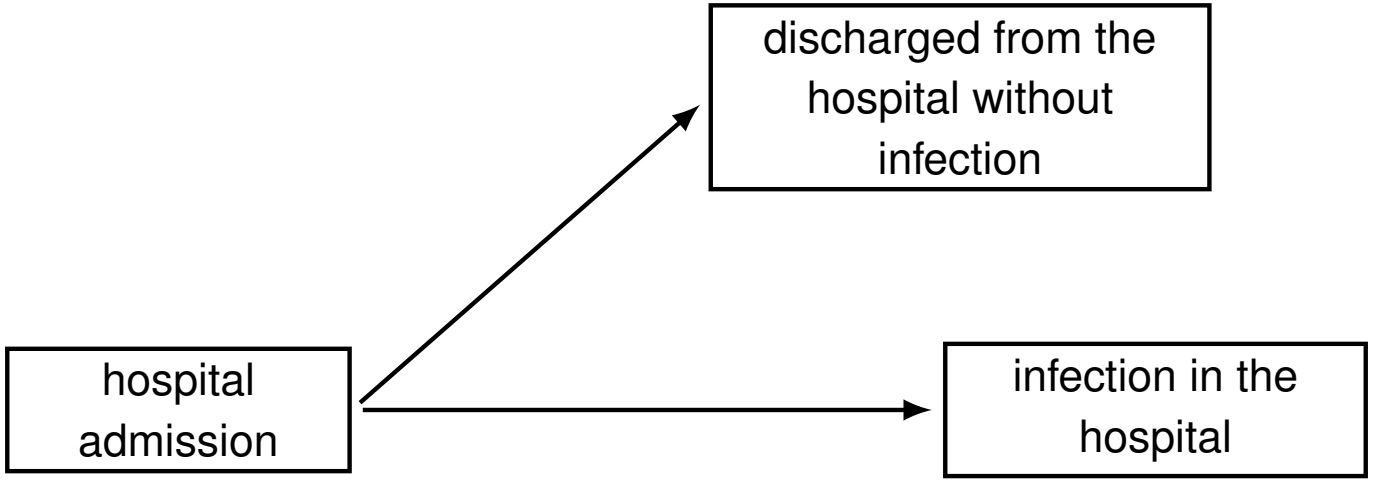


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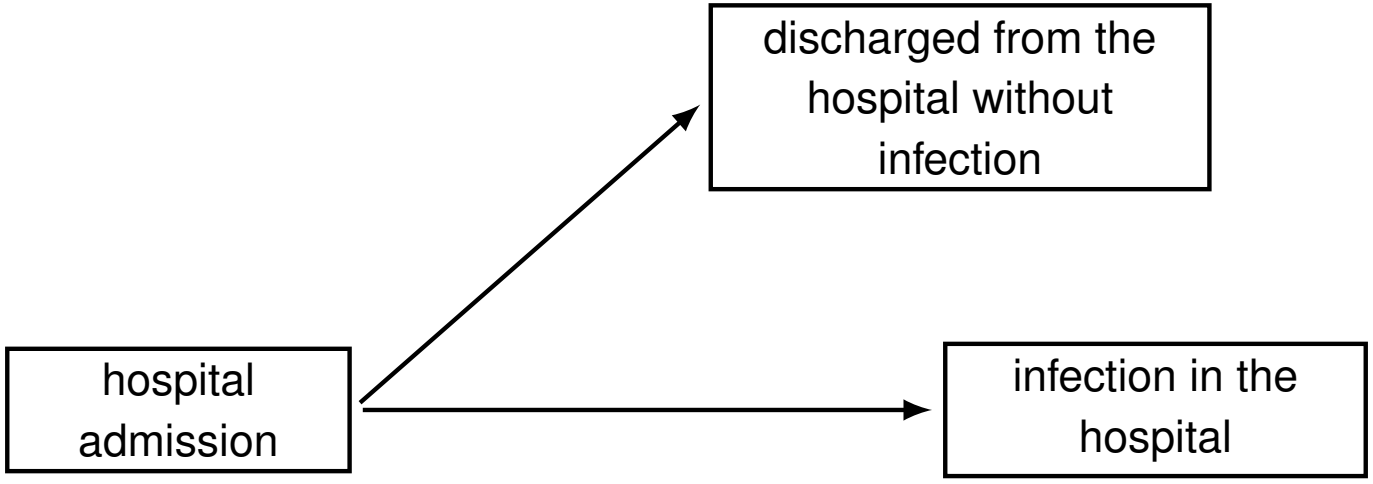


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# Estimation, no censored data

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|---|---|---|---|---|---|---|---|---|
| infection | 1 | 2 | 6 | 11 | 9 | 11 | 2 | 18 |
| cumulative | 1 | 3 | 9 | 20 | 29 | 40 | 42 | 60 |
| discharge | 5 | 9 | 6 | 6 | 9 | 12 | 4 | 35 |
| cumulative | 5 | 14 | 20 | 26 | 35 | 47 | 51 | 86 |

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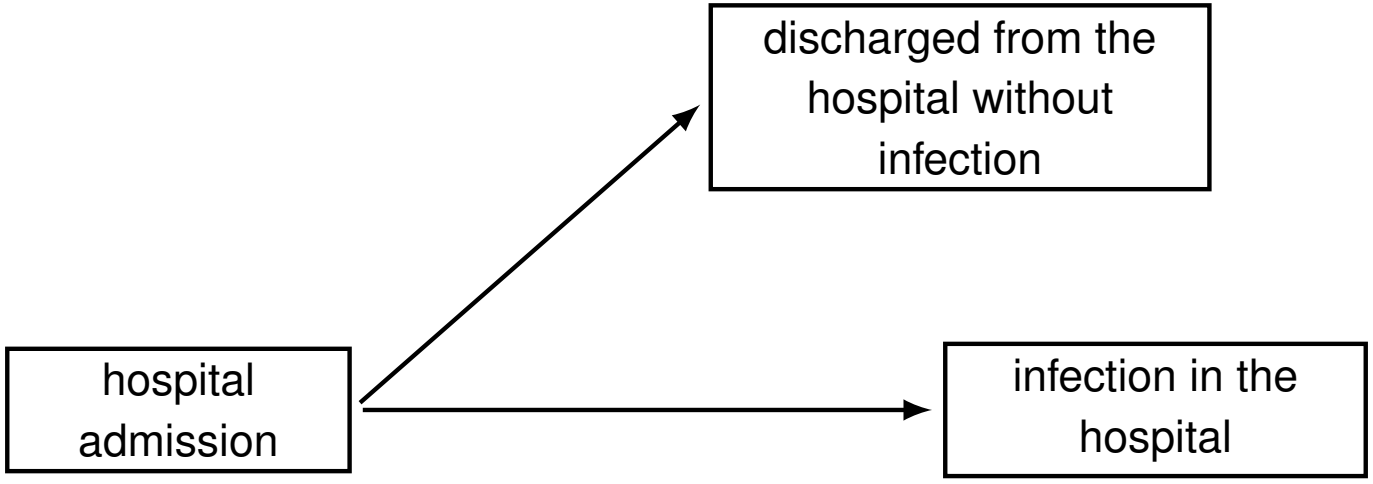


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- Which of two hospitals has higher risk may depend on type of question

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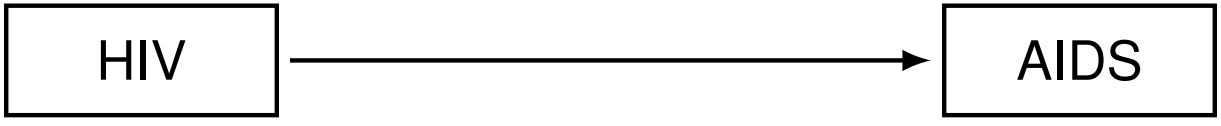


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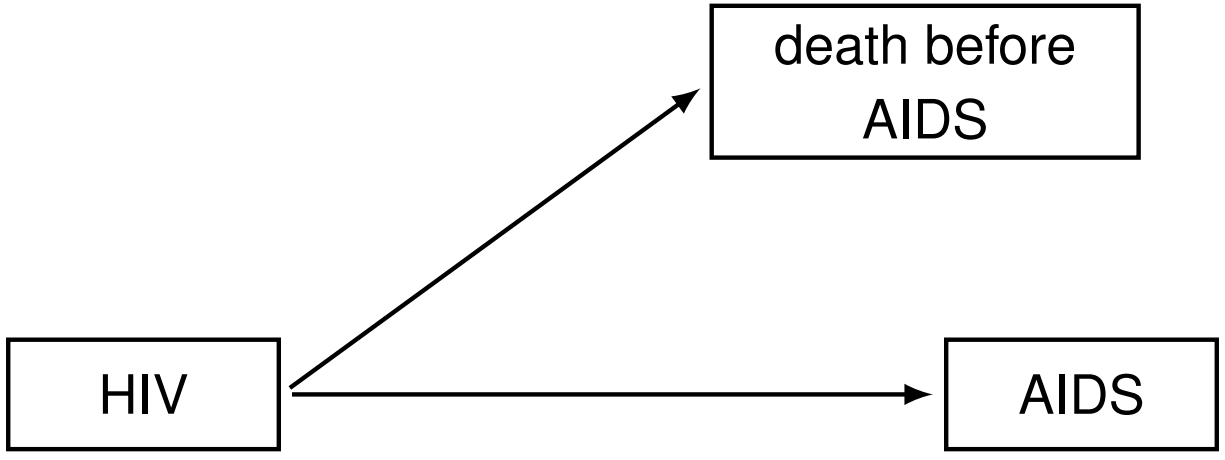


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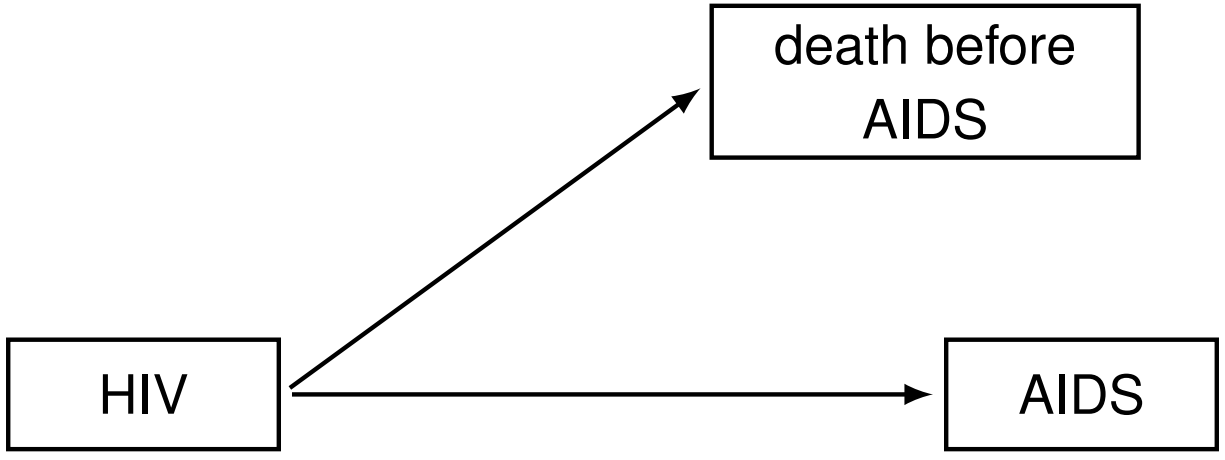


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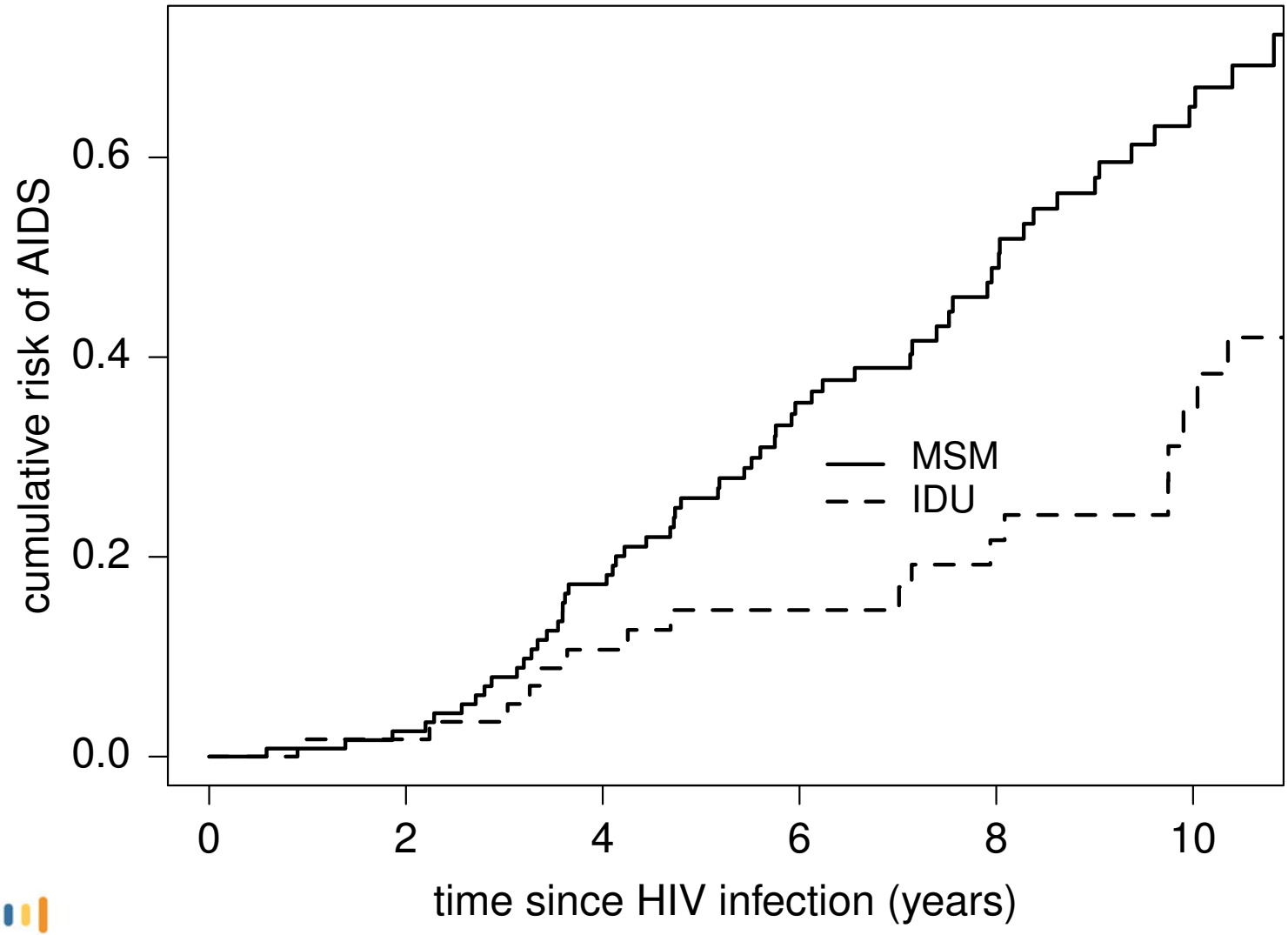
  Interest in etiology and marginal distribution

# Kaplan-Meier: IDU much slower progression ($p = 0.001$)



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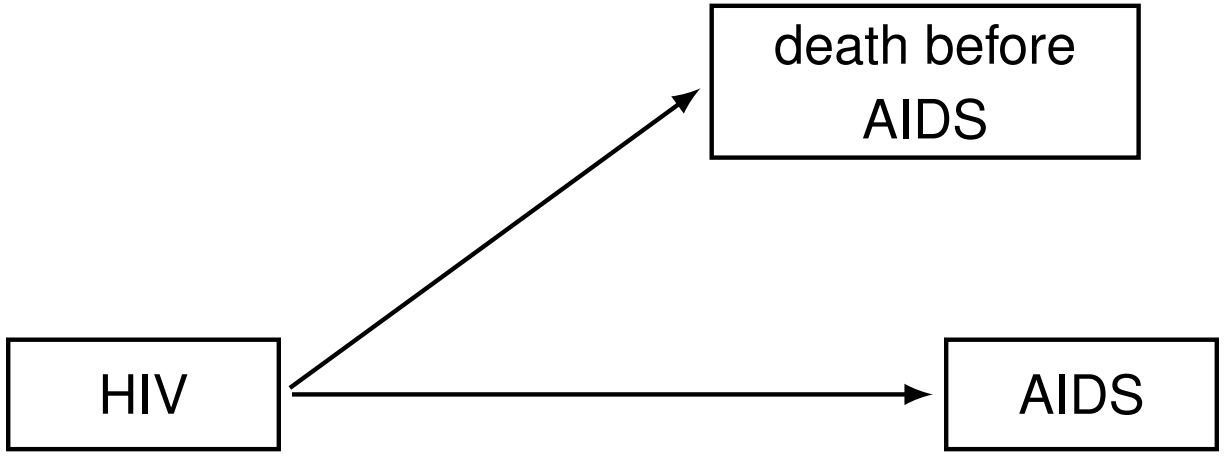


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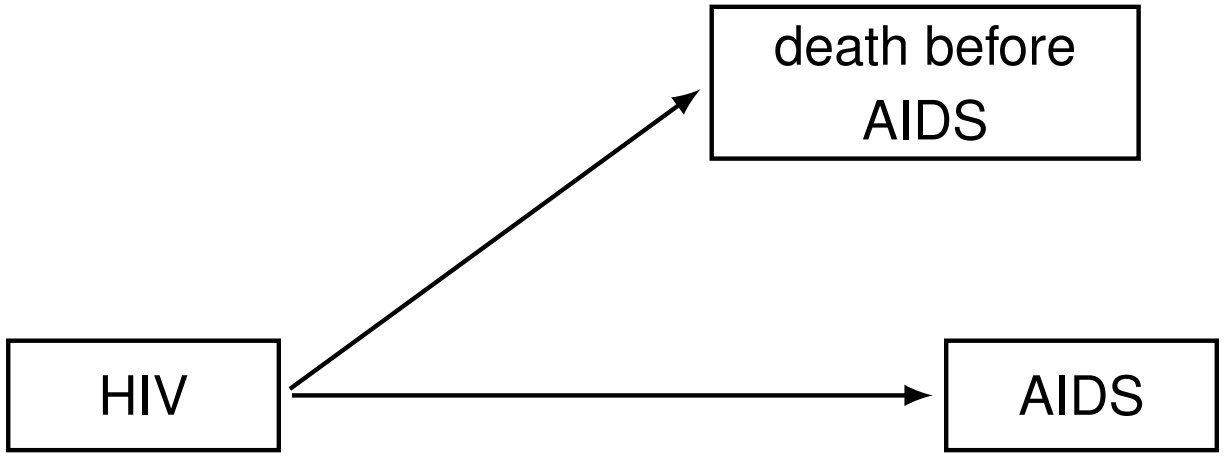


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- Interest in time to AIDS if there were no pre-AIDS death. Interest in etiology and marginal distribution
- Kaplan-Meier: leave risk set at death before AIDS
  Assumption: deaths equal AIDS risk

# Explanation: dependent censoring

- Extra information on cause of death before AIDS

| | IDU | MSM |
|---|---|---|
| Reason of death | Number | |
| HIV related infections | 3 | 0 |
| overdose/suicide | 6 | 0 |
| violence/accident | 2 | 0 |
| liver cirrhosis | 2 | 0 |
| cancer | 0 | 1 |
| heart attack | 0 | 1 |
| unknown | 4 | 3 |

- Some causes of pre-AIDS death in IDU related to AIDS progression. Censoring close to AIDS, hence estimate for IDU too optimistic

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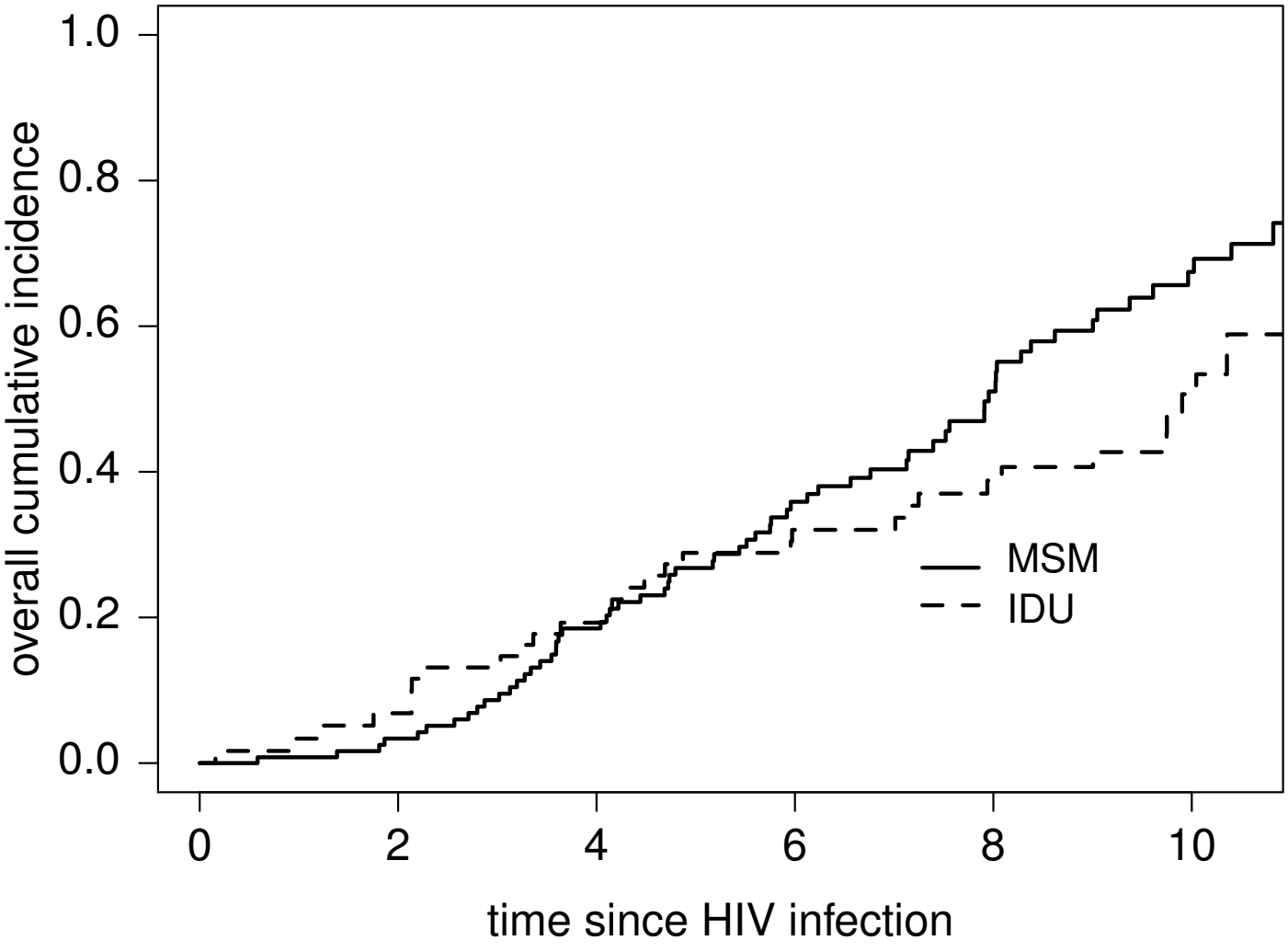
## i) Combine AIDS and pre-AIDS death




Overall time-to-event distribution (both event types combined)

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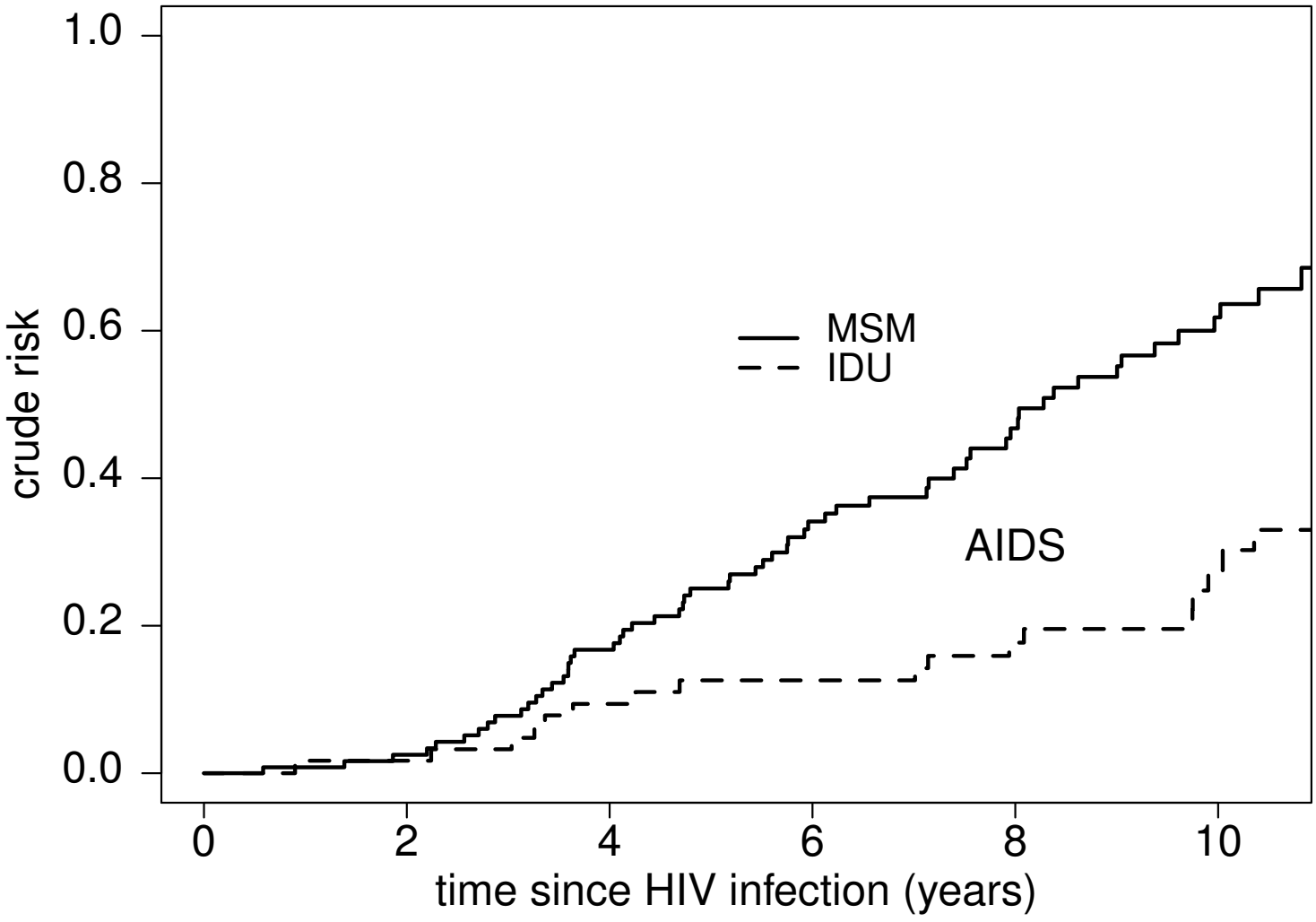
- What if: i) deaths would have developed AIDS right after
- What if: ii) deaths would never have developed AIDS

## ii) AIDS-specific cumulative incidence

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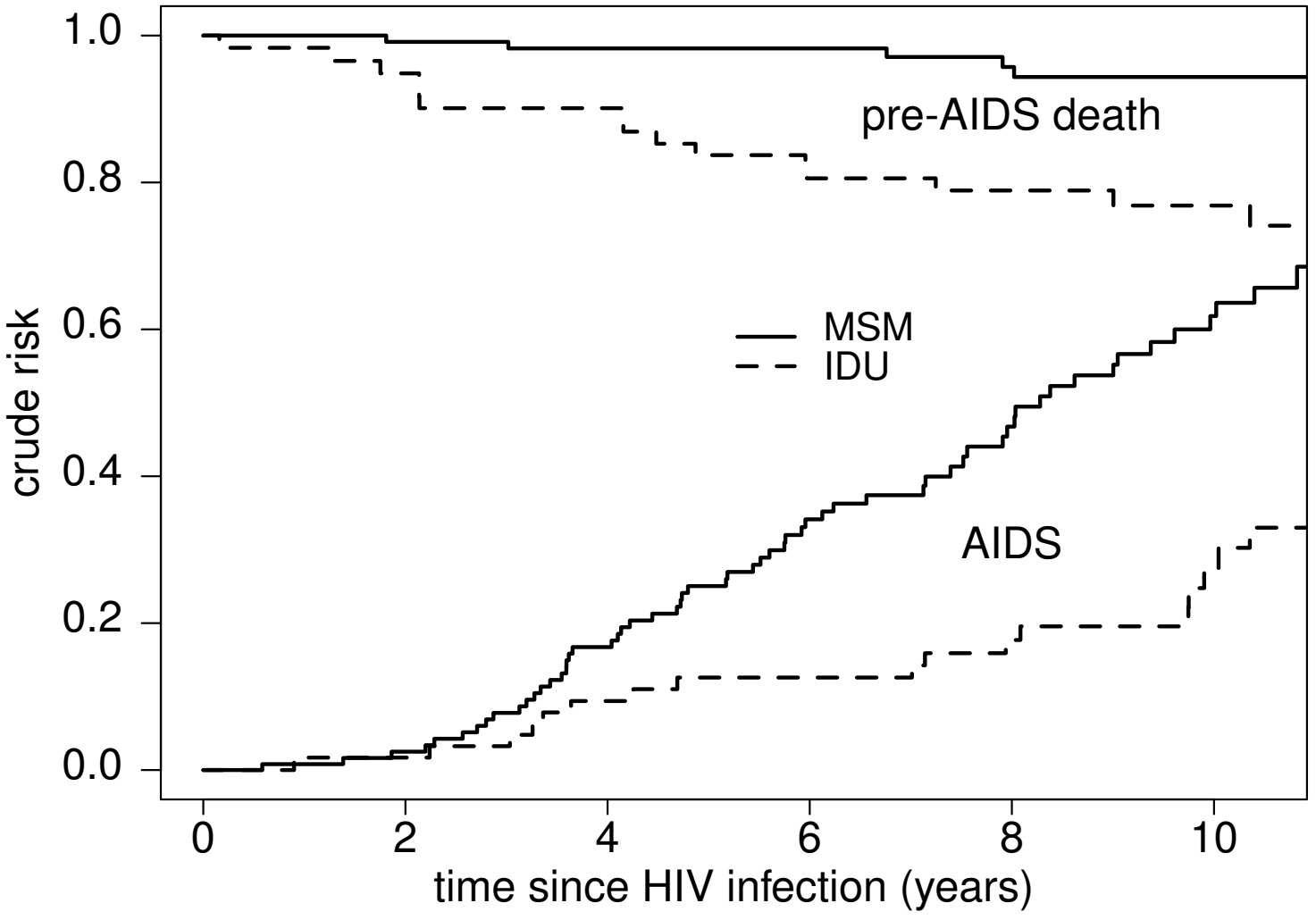
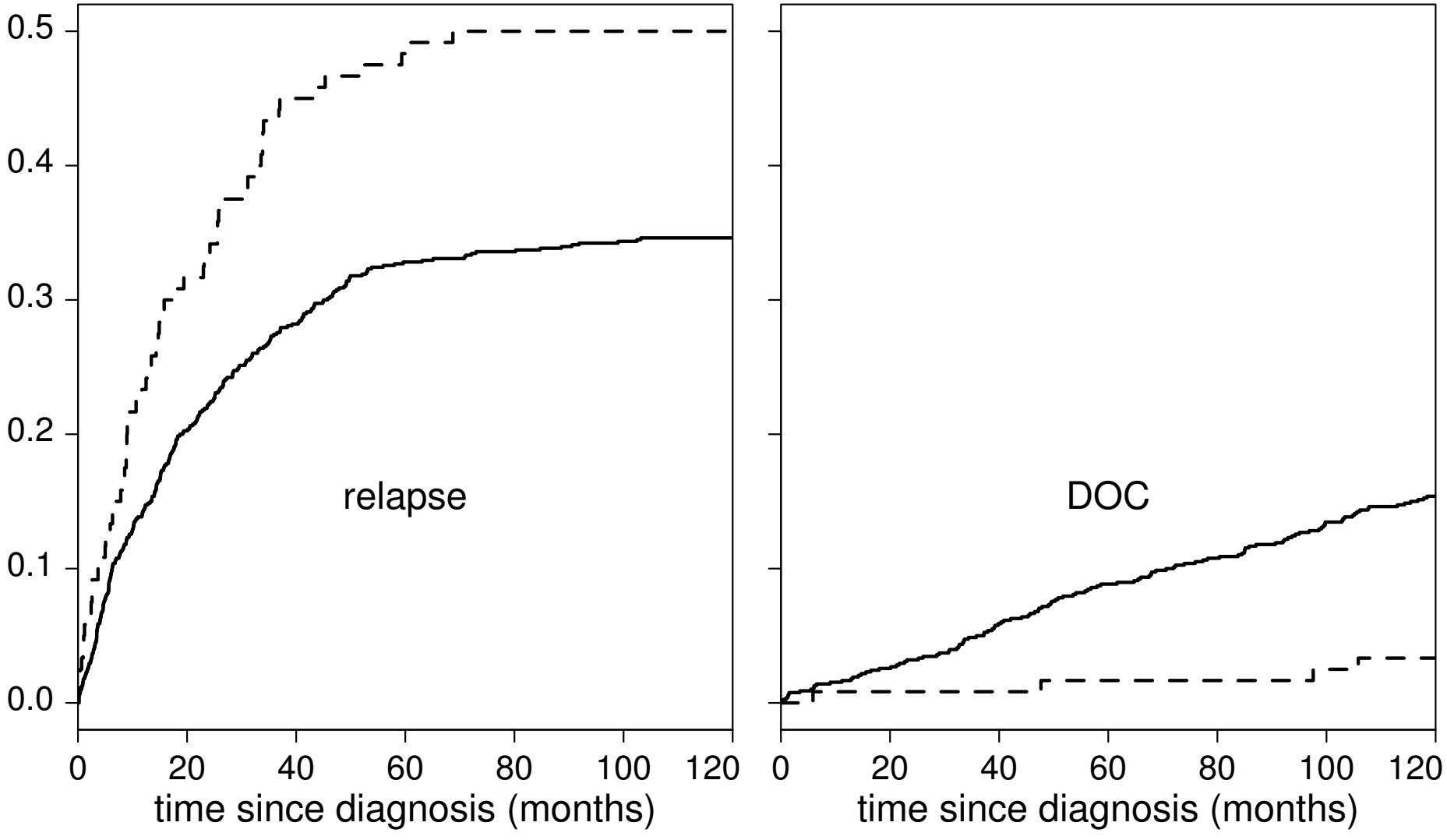



AIDS-specific cumulative incidence (pre-AIDS death prevents AIDS)

# IV: Bladder cancer; relapse, death other causes (DOC) competing




Left: relapse. Solid: male; dashed: female

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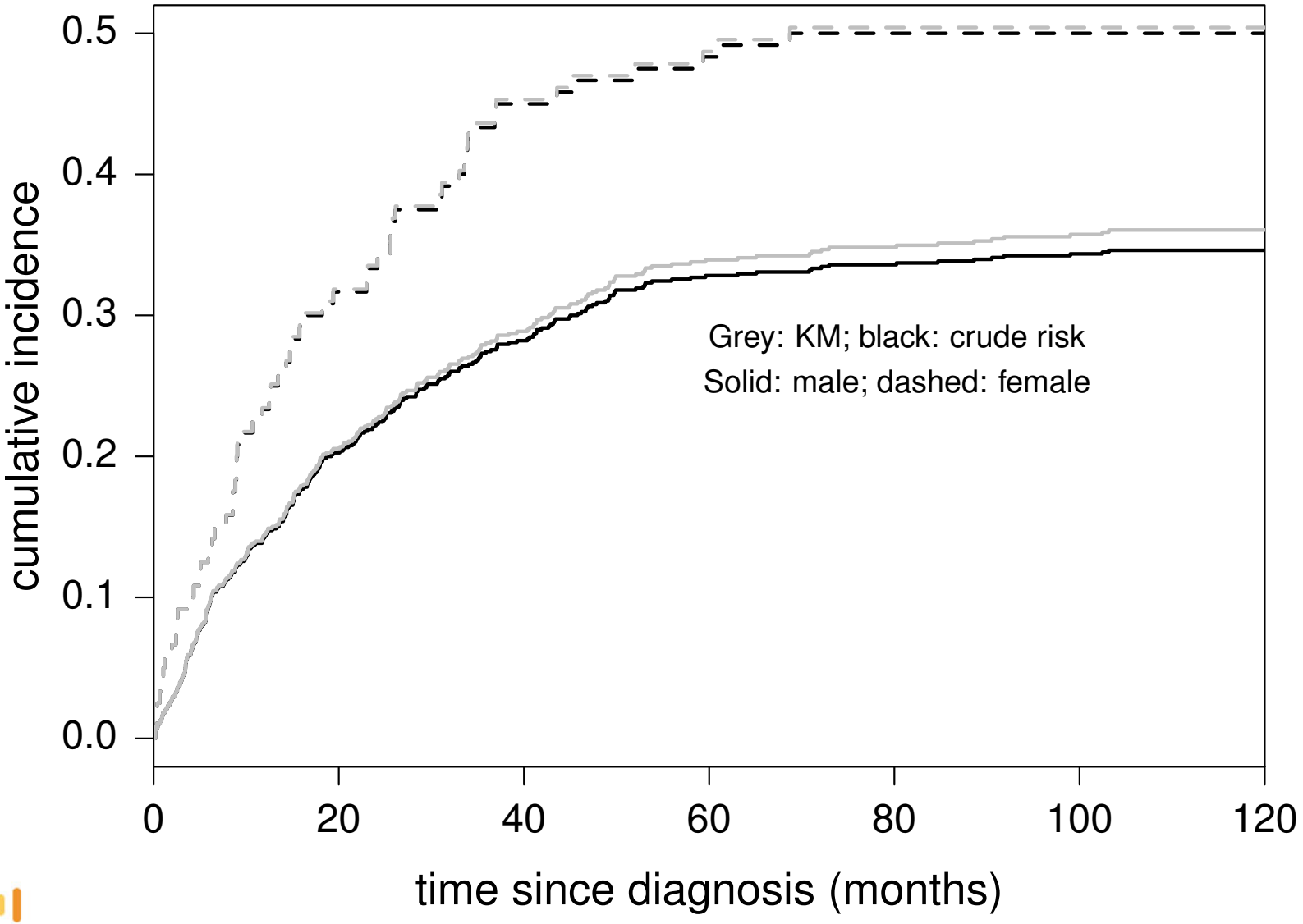

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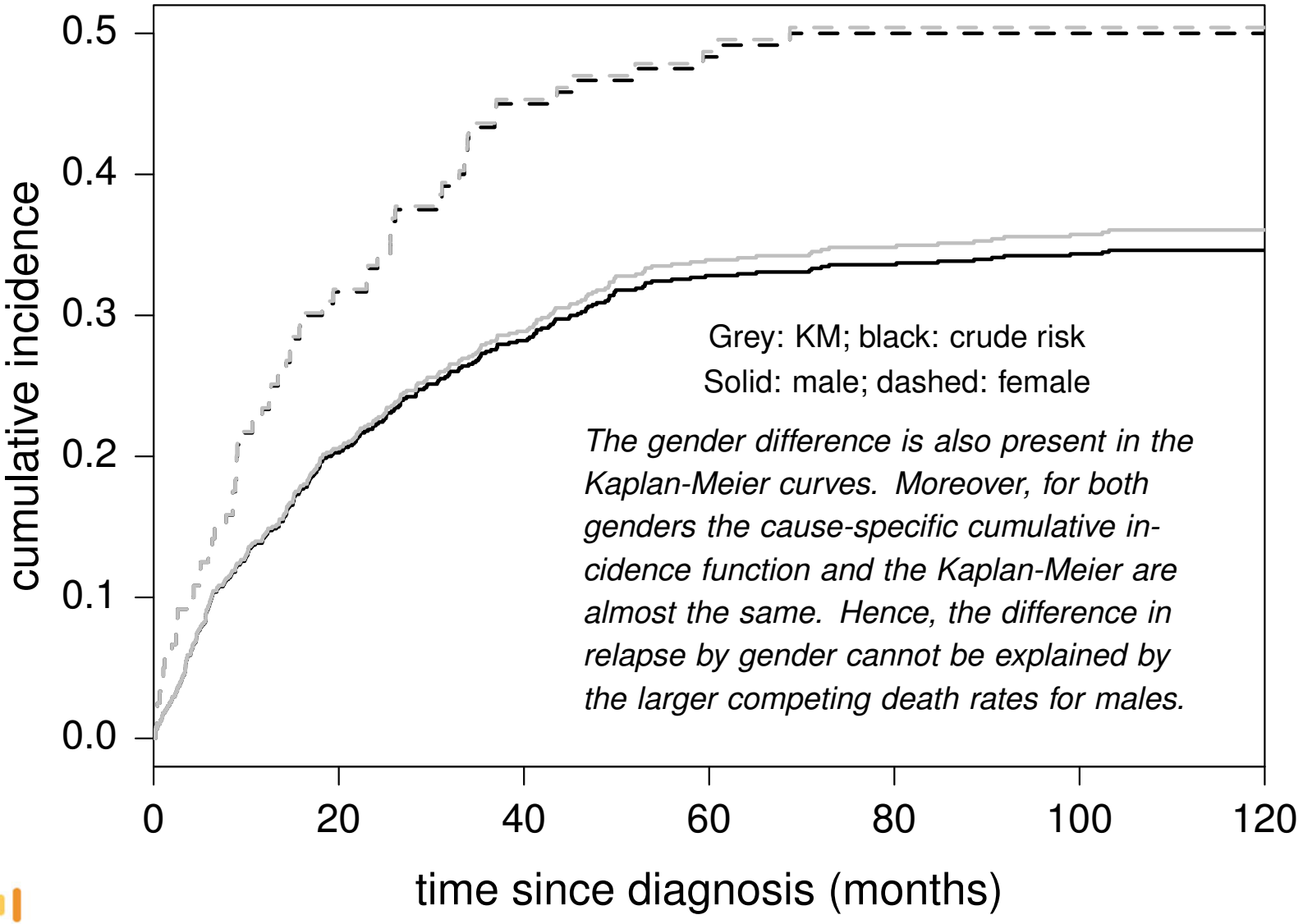

# Competing risks versus marginal analysis

- Is setting without competing risk realistic or completely hypothetical? Can occurrence of competing risk be prevented?
  - Biological event: disease onset, death from “natural” cause
  - Human intervention: start of treatment, discharge, death from suicide
- Can the marginal distribution be estimated? Do those with the competing risk have the same event risk as the ones that remain event free? Is censoring due to competing risks independent?
- Examples:
  - Hospital infection and discharge
  - AIDS and pre-AIDS death
  - Relapse and DOC

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- Main Quantities
- Nonparametric Estimation
- Regression

Which Approach to Choose?

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**Which Approach to Choose?**
- Marginal versus competing risks
- Which competing risks approach to choose?

## Setup and notation

- Competing risks: type $E \in \{1, \ldots, K\}$
- $T \sim F$ time to event (of any type); $F(t) = \mathrm{P}(T \leq t)$
- Overall hazard $h$: $\mathrm{P}(T > t) = \exp\{-\int_0^t h(s)ds\}$
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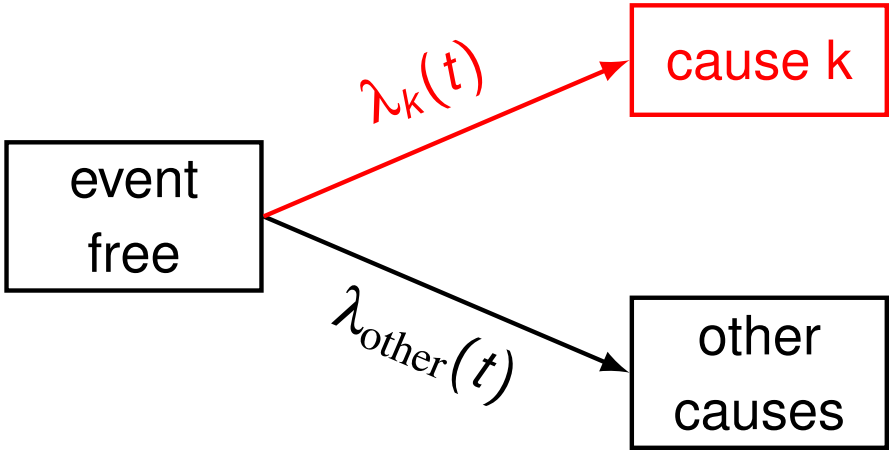
- cause-specific cumulative incidence : $F_k(t) = \mathrm{P}(T \leq t, E = k)$

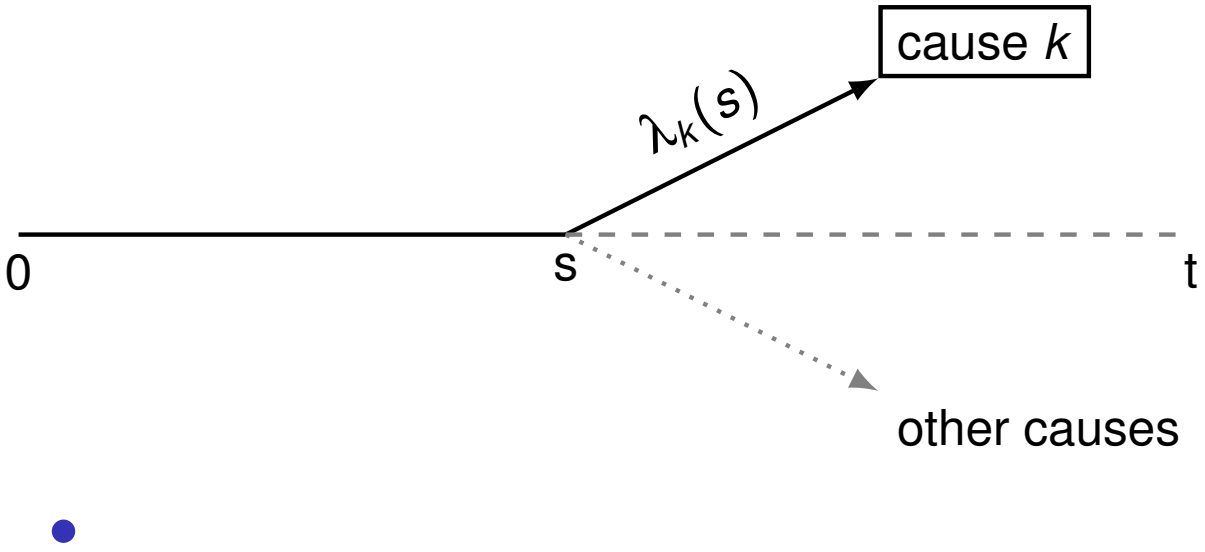
# The multi-state approach: cause-specific hazard




- Transition rate to cause k. For continuous distribution:

$$\lambda_k(t) = \lim_{\Delta t \downarrow 0} \frac{\mathrm{P}(t \leq T < t + \Delta t, E = k \mid T \geq t)}{\Delta t}$$

# From hazard to cumulative scale $\mathrm{P}(T \leq t, E = k)$



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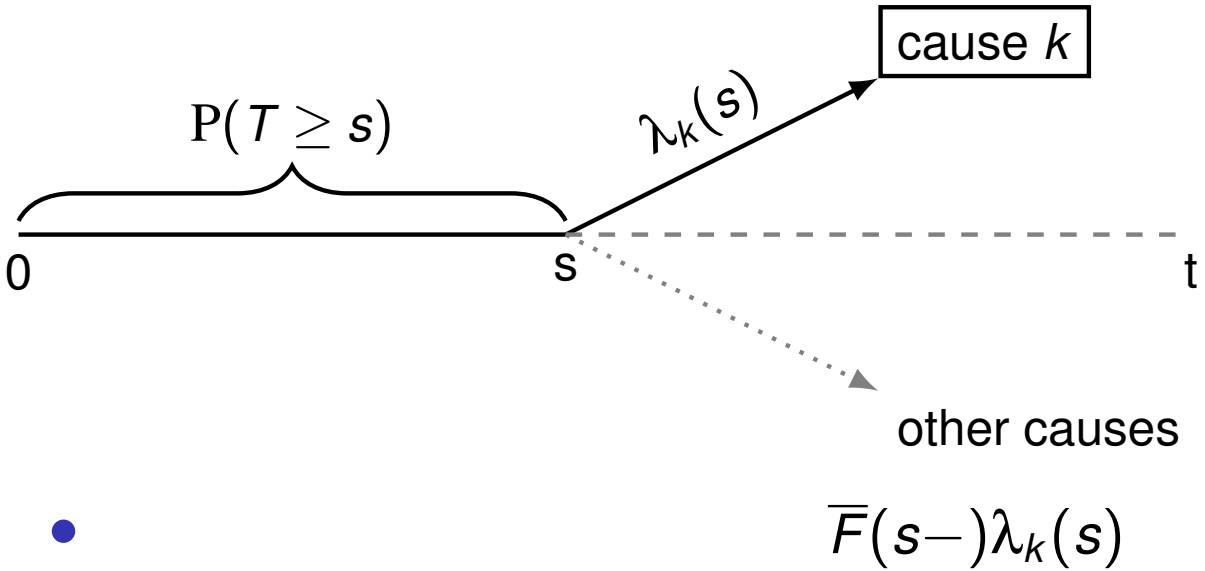


- $\overline{F}(s-)\lambda_k(s)$

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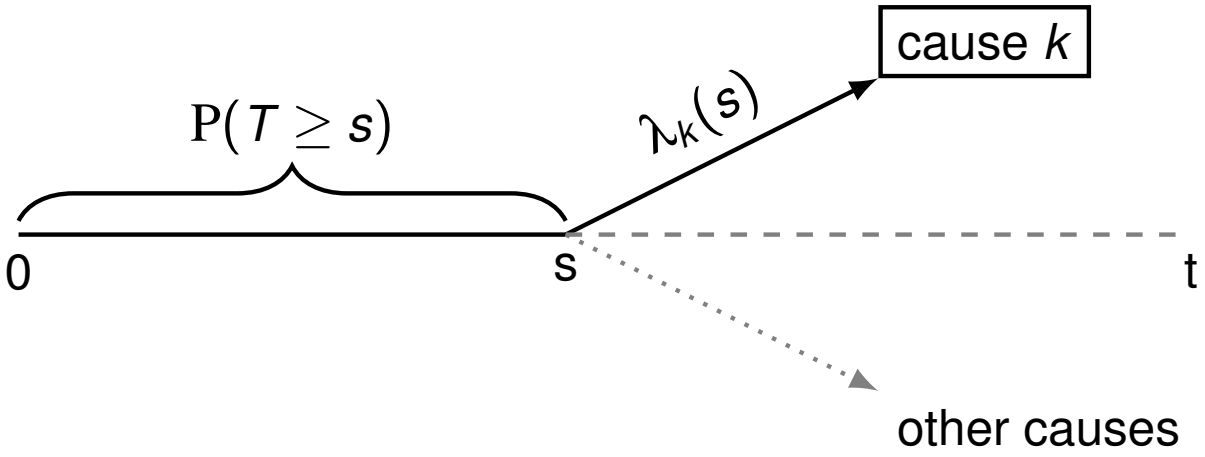


- $F_k(t) = \mathrm{P}(T \leq t, E = k) = \int_0^t \overline{F}(s-)\lambda_k(s)ds$

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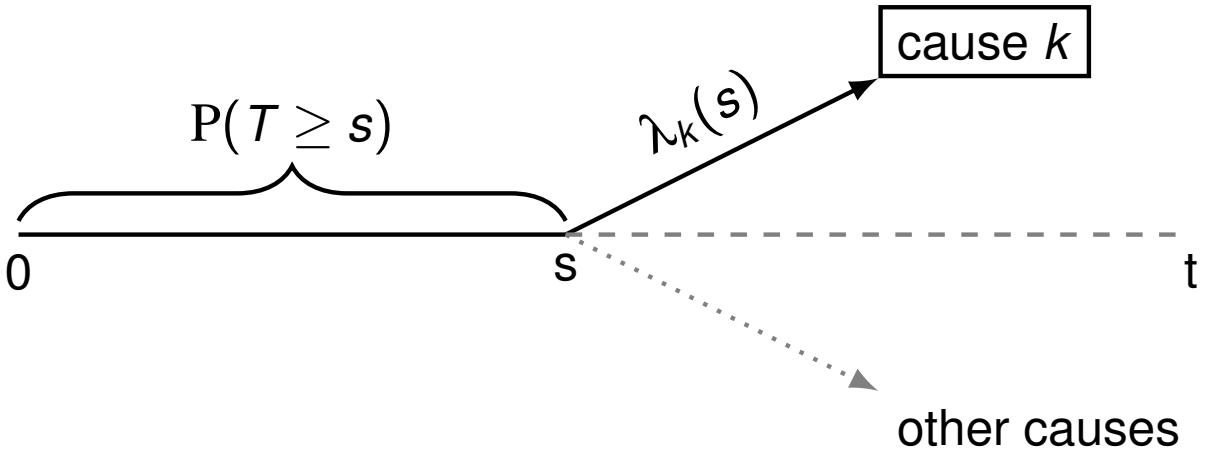


- $F_k(t) = \mathrm{P}(T \leq t, E = k) = \int_0^t \overline{F}(s-)\lambda_k(s)ds$
- Depends on all cause-specific hazards via overall "survival"

$$\overline{F}(s) = \exp\left\{-\int_0^s h(u)du\right\} = \exp\left\{-\sum_{e=1}^{K}\int_0^s \lambda_e(u)du\right\}$$

- $\Longrightarrow \lambda_k$ does not uniquely specify $\mathrm{P}(T \leq t, E = k)$

# The subdistribution approach

# Setup and notation

- Competing risks: type $E \in \{1, \ldots, K\}$

- cause-specific cumulative incidence : $F_k(t) = \mathrm{P}(T \leq t, E = k)$
- Subdistribution random variable $T_k \sim F_k$:
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# Rates and risks in competing risks setting

| | hazard | | cumulative | |
|---|---|---|---|---|
| competing risks | marginal | $\lambda^m$ | net risk | $F^m(t)$ |
| | | | marginal survival function | |
| | | | marginal cumulative incidence | |
| | cause-specific | $\lambda_k$ | no corresponding quantity | |
| | subdistribution | $h_k$ | crude risk | $F_k(t)$ |
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| combined | overall | $h$ | overall risk | $F(t)$ |
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# Outline

**Competing Risks; When**

**Competing Risks; How**

- Main Quantities
- Nonparametric Estimation
- Regression

**Which Approach to Choose?**

- Marginal versus competing risks
- Which competing risks approach to choose?

# Observed data

$$\{(x_1, e_1\delta_1), \ldots, (x_N, e_N\delta_N)\}$$

- $x_i = \min\{t_i, c_i\}$, $\delta_i = \{t_i \leq c_i\}$, $e_i \in \{1, \ldots, K\}$
- $t_{(i)}$ ordered unique event times of any type

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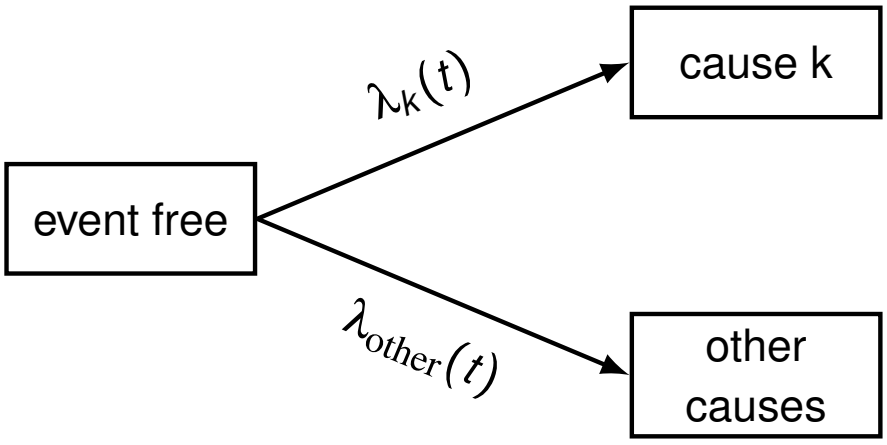
# Cause-specific hazard

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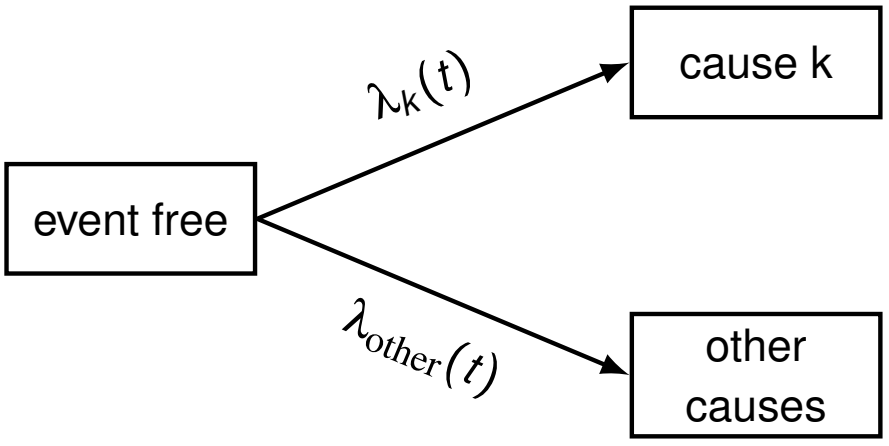


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- Standard rate estimation. Same estimator as marginal hazard, but different interpretation, unless censoring due to competing risks is non-informative

# Aalen-Johansen estimator of $F_k$

- Plug-in estimator based on $F_k(t) = \int_0^t \mathrm{P}\{T \geq s\}\lambda_k(s)ds$:

$$\widehat{F}_k^{\mathrm{AJ}}(t) = \sum_{i:t_{(i)} \leq t} \widehat{\overline{F}}^{\mathrm{PL}}(t_{(i)}-) \times \widehat{\lambda}_k(t_{(i)}) \text{ with}$$

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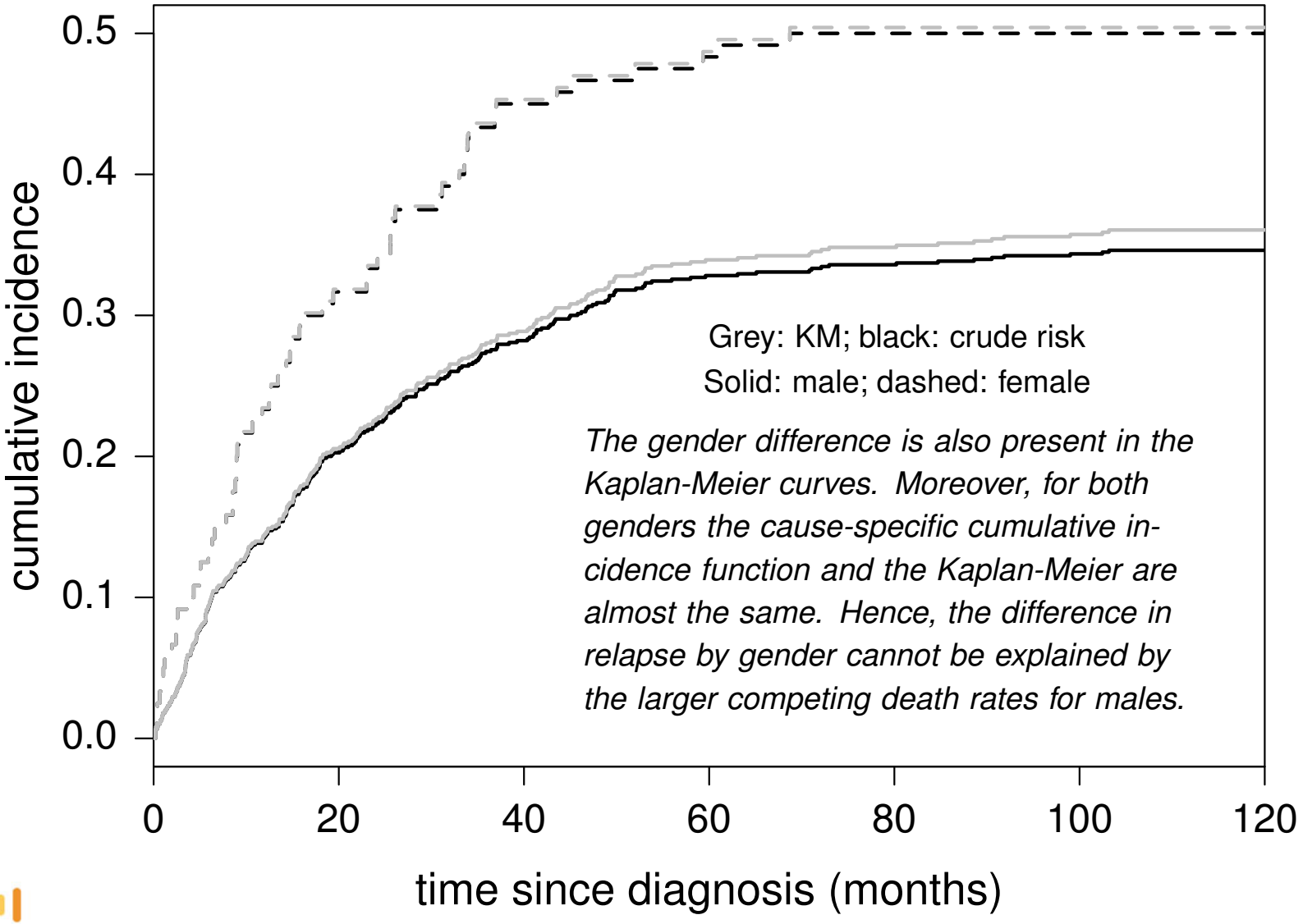
- Single event type: equal to Kaplan-Meier
- Competing risks: same hazard estimate as for marginal distribution, but cumulative quantity different

# IV: Bladder cancer; relapse, DOC competing



# IV: Answer

- The Kaplan-Meier tries to compare the marginal distribution of time to relapse for males and females. Only valid if DOC is noninformative for relapse.
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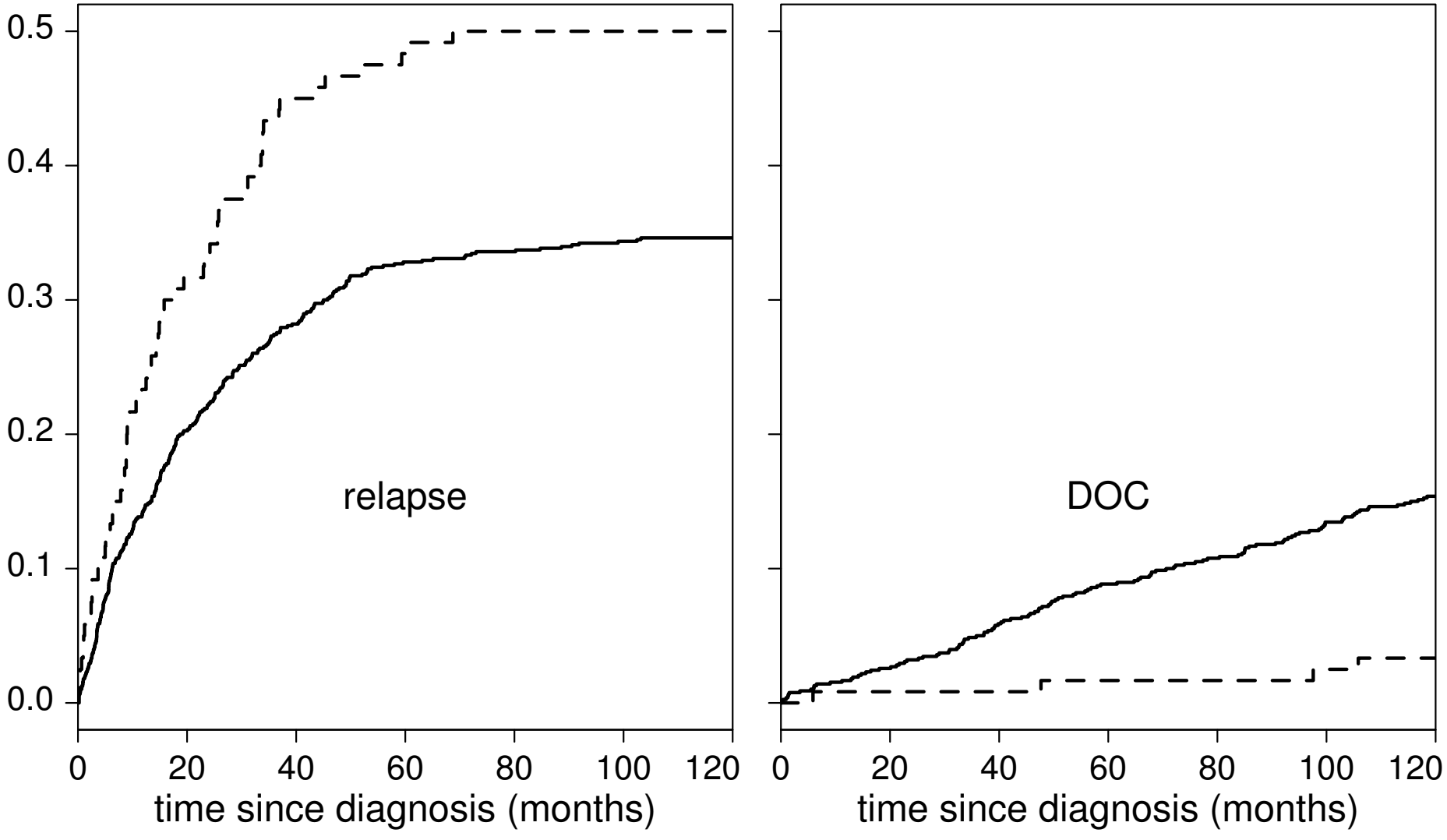


Left: relapse. Solid: male; dashed: female

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- If we combine both event times, the curves for males and females will become similar. Would estimate marginal hazard if every person that died would have progressed on the next day.
- All we can conclude is that females have a higher relapse-specific cumulative incidence than males. And females have a lower DOC-specific incidence than males.

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- $t_{(i)}$ ordered unique event times of any type
- $r(t_{(i)})$ number observed at risk
- $r^*(t_{(i)})$ number in risk set (for subdistribution hazard)
- $d_k(t_{(i)})$ number of events at $t_{(i)}$ of type $k$
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## Subdistribution $\widehat{F}_k$: product-limit estimator

$$\widehat{F}_k^{\mathrm{PL}}(t) = \prod_{i:t_{(j)} \leq t} \left\{ 1 - \widehat{h}_k(t_{(j)}) \right\}$$

with

$$\widehat{h}_k(t_{(j)}) = \frac{d_k(t_{(j)})}{r^*(t_{(j)})}$$

**No censoring:** individuals with competing event remain in risk set forever. Small change in data, standard software

# Estimation, no censored data

| week | 0-1 | 1-2 | 2-3 | 3-4 | 4-5 | 5-6 | 6-7 | $>7$ |
|---|---|---|---|---|---|---|---|---|
| infection | 1 | 2 | 6 | 11 | 9 | 11 | 2 | 18 |
| cumulative | 1 | 3 | 9 | 20 | 29 | 40 | 42 | 60 |
| discharge | 5 | 9 | 6 | 6 | 9 | 12 | 4 | 35 |
| cumulative | 5 | 14 | 20 | 26 | 35 | 47 | 51 | 86 |

- Subdistribution. Estimated as frequency of events:

  $\widehat{P}(\text{infection} \leq 6\,\text{weeks}) = 40/146$

  $\widehat{P}(\text{discharge} \leq 6\,\text{weeks}) = 47/146$

  Individuals with competing event remain in denominator, competing event ignored in estimation

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**General censoring:** Estimate time-to-censoring distribution, then

- multiply impute censoring times for those with competing event
- reweight them by probability to remain uncensored

## Right Censored Data

$$\widehat{h_k}(t_{(i)}) = \frac{d_k(t_{(i)})}{r^*(t_{(i)})}$$

Contribution $\omega_l(t_{(i)})$ of individual $l$ to the risk set $r^*(t_{(i)})$ is:

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estimate of $\mathrm{P}\{C \geq t_{(i)} | C \geq t_{(j)}\}$ :

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- $\widehat{\bar{\Gamma}}$: reverse role of event time $T_i$ and censoring $C_i$:

$$\widehat{\bar{\Gamma}}(t) = \prod_{j:c_{(j)} \leq t} \left\{ 1 - \frac{m_j}{r(c_{(j)})} \right\}$$

$m_j$: number of censorings at $c_{(j)}$

# Subdistribution $\widehat{F}_k$: ECDF estimator

- Without censoring

$$\widehat{F}_k^{\mathrm{EC}}(t) = \frac{\#\{t_i \leq t\}}{N} = \sum_{t_{(j)} \leq t} \frac{d_k(t_{(j)})}{N}.$$

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- Right censored data

$$\widehat{F}_k^{\mathrm{EC}}(t) = \frac{1}{N} \sum_{t_{(j)} \leq t} \frac{d_k(t_{(j)})}{\widehat{\overline{\Gamma}}(t_{(j)}-)}$$

# Equivalence

If $\widehat{\overline{\Gamma}}$ based on the PL-form, then we have

$$\widehat{F}_k^{\,\mathrm{AJ}} \equiv \widehat{F}_k^{\,\mathrm{PL}} \equiv \widehat{F}_k^{\,\mathrm{EC}}$$

(Geskus 2011, Biometrics)

$$\widehat{F}_k^{\,\mathrm{AJ}}(t) = \sum_{i:t_{(i)} \le t} \widehat{\overline{F}}^{\mathrm{PL}}(t_{(i)}-) \times \widehat{\lambda}_k(t_{(i)})$$

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# Estimators in competing risks setting

| hazard | estimate | estimate cumulative incidence |
|---|---|---|
| marginal | $\left\{\widehat{\lambda}(t) = d_k(t)/r(t)\right\}$ | $\left\{\widehat{\overline{F^m}}^{\mathrm{PL}}(t) = \prod_{t_{(j)} \le t}\left[1 - \widehat{\lambda}(t_{(j)})\right]\right\}$ |
| cause-specific | $\widehat{\lambda_k}(t) = d_k(t)/r(t)$ | $\widehat{F_k}^{\mathrm{AJ}}(t) = \sum_{t_{(j)} \le t} \widehat{\overline{F}}^{\mathrm{PL}}(t_{(j)}-)\widehat{\lambda_k}(t_{(j)})$ |
| subdistribution | $\widehat{h_k}(t) = d_k(t)/r^*(t)$ | $\widehat{\overline{F_k}}^{\mathrm{PL}}(t) = \prod_{t_{(j)} \le t}\left[1 - \widehat{h_k}(t_{(j)})\right]$ |
| | | $\widehat{F_k}^{\mathrm{EC}}(t) = \frac{1}{N}\sum_{t_{(j)} \le t} \frac{d_k(t_{(j)})}{\widehat{\overline{\Gamma}}(t_{(j)}-)}$ |
| overall | $\widehat{h}(t) = d(t)/r(t)$ | $\widehat{\overline{F}}^{\mathrm{PL}}(t) = \prod_{t_{(j)} \le t}\left[1 - \widehat{h}(t_{(j)})\right]$ |

# Outline

**Competing Risks; When**

**Competing Risks; How**

- Main Quantities
- Nonparametric Estimation
- Regression

**Which Approach to Choose?**

- Marginal versus competing risks
- Which competing risks approach to choose?

# Cause-specific hazard

- Completely standard, e.g. Cox model

$$\lambda_k(t \mid \mathbf{Z}_i) = \lambda_{k,0}(t) \exp(\beta_k^\top \mathbf{Z}_i).$$

  - Censor individuals with a competing event
  - SE completely standard as well
  - Interpretation is different: cause-specific event rate among event-free individuals
  - Not a marginal hazard, unless competing risks independent conditionally on covariables

# Subdistribution hazard

- Proportional subdistribution hazards (Fine and Gray model)

$$h_k(t \mid \mathbf{Z}_i) = h_{k,0}(t) \exp(\beta_k^\top \mathbf{Z}_i) .$$

  - Estimation: those with competing event remain in risk set, with weight reflecting probability to remain uncensored
  - SE completely standard
    Simulation study (Geskus 2011, Biometrics): sandwich estimator as suggested by Fine and Gray performed worse
  - Standard software with time-varying individual weights
  - Interpretation difficult, but direct relation with cause-specific cumulative incidence

# Cause-specific cumulative incidence

- (Proportional odds) logistic regression

$$\text{logit}[\text{P}(T_k \leq t \mid \mathbf{Z}_i)] = \log[\pi_{k,0}(t)] + \beta_k^\top \mathbf{Z}_i$$

translates to the cause-specific cumulative incidence as

$$\text{P}(T_k \leq t \mid \mathbf{Z}_i) = \frac{\pi_{k,0}(t)\exp(\beta_k^\top \mathbf{Z}_i)}{1+\pi_{k,0}(t)\exp(\beta_k^\top \mathbf{Z}_i)}.$$

- Estimation: estimating equations, with weights reflecting probability to remain uncensored
  - Scheike *et al.* (2008): event weighted as in $\widehat{F}_k^{\text{EC}}$
  - Eriksson *et al.* (2015): weights as in $\widehat{h}_k$
  - Blanche *et al.* (2023): individuals weighted as in $\widehat{F}_k^{\text{EC}}$
- SE based on sandwich estimator

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# Marginal distribution

- Often via (marginal) hazard, basis for Kaplan-Meier estimate of cumulative incidence/net risk
- Assumption: Censored individuals (including due to competing risk) can be represented by the ones that remain at risk. Being censored should give no information on residual time to event

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- Otherwise Kaplan-Meier has no meaning.
  Does not describe survival in (hypothetical) world with competing event removed, unless we know that censoring is independent
- Extra information may allow to show informative/dependent censoring (IDU and pre-AIDS death), but independence can never be tested for

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- Subdistribution hazard: one-to-one relation with crude risk

# Marginal or competing risks?

- Example I: spectrum in COD
  Competing risks; marginal analysis completely hypothetical
- Example II: staphylococcus infection in hospital
  - Marginal: what if everyone would stay in hospital
  - Competing risks: how many infections are observed in hospital
- Example III: difference in natural history between IDU en MSM
  Marginal analysis, but difficult to perform
- Example IV: bladder cancer relapse and DOC
  Marginal interpretation, but does it make sense?
  Can we eliminate DOC? Is their mechanism completely separate from mechanism leading to relapse?

# Outline

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# Cause-specific hazard, subdistribution hazard or crude risk?

- Cause-specific may often be closer to causal effects, but any hazard is problematic as causal estimand
- Cumulative scale combination of etiology and effect on other event types.
  “In the end we all die, but cause of death may be different”
  “Impact” instead of “effect”
- Cumulative estimate final aim for prediction, but each may serve as basis for model
- Subdistribution hazard directly relates to cumulative scale
  Regression: impact on cumulative scale via parameters
- Some suggest to quantify both hazards

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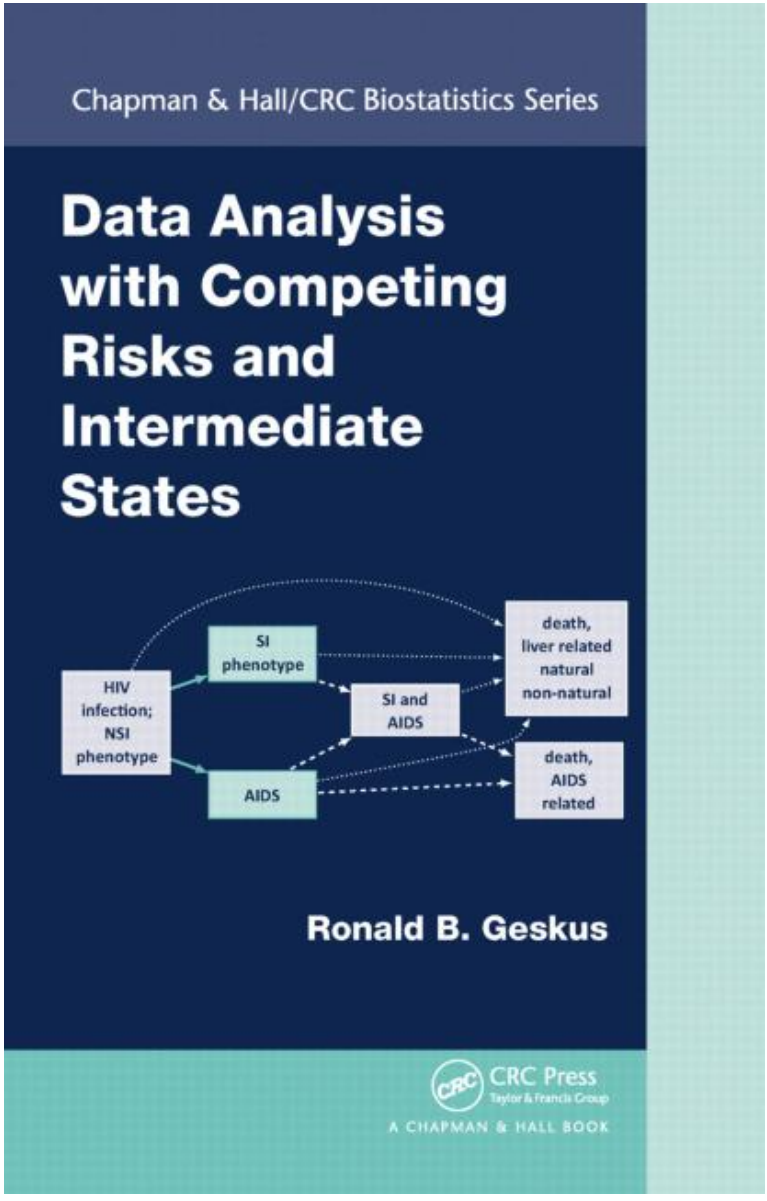

# THANKS!

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