Sciences Economiques et Sociales de la Santé
& Traitement de l'Information Médicale

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Competing risks, analysis and interpretation

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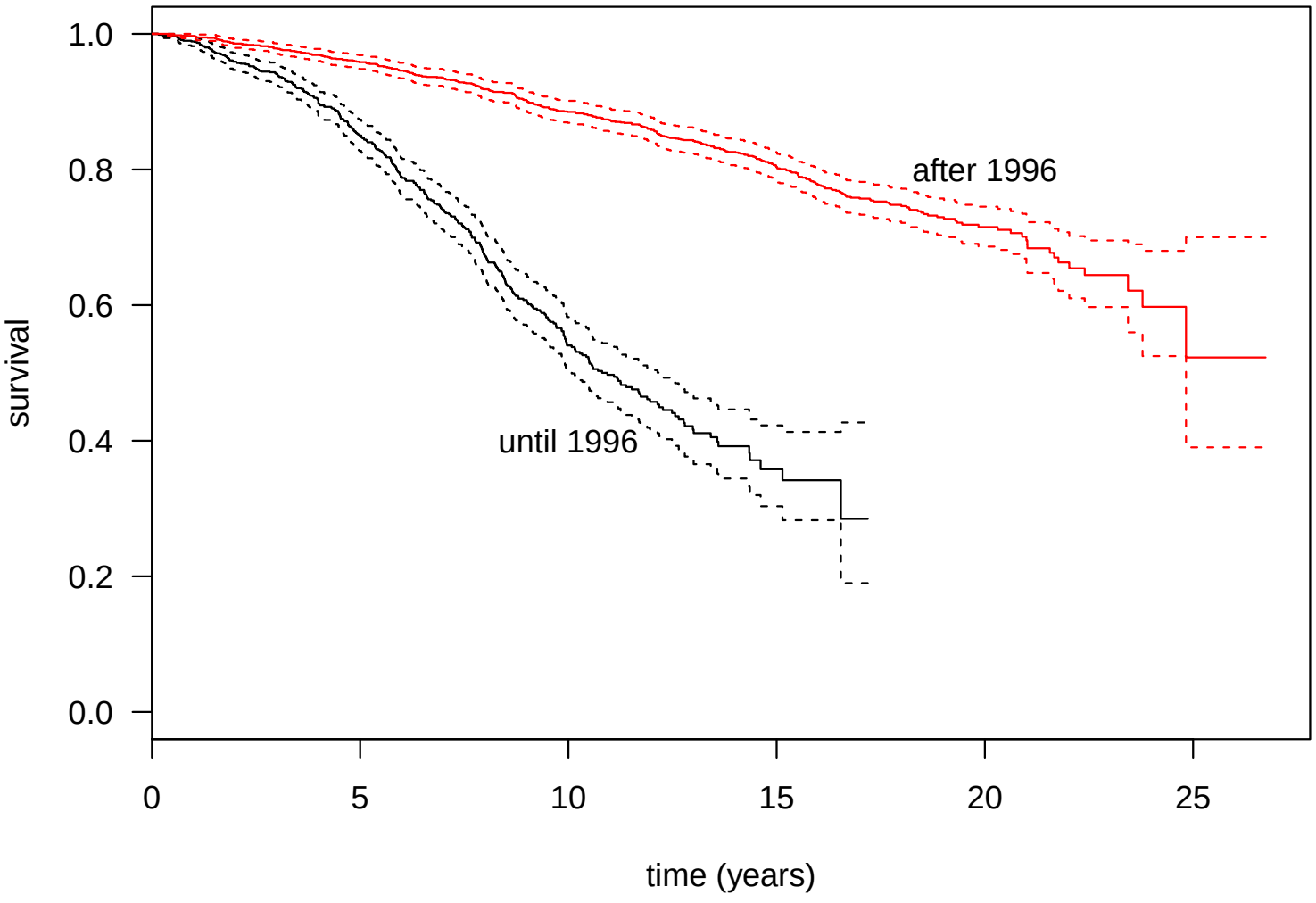
Competing risks, analysis and interpretation

SESSTIM
December 18, 2020

Ronald Geskus
Oxford University Clinical Research Unit (OUCRU)
Hospital for Tropical Diseases, Ho Chi Minh City, Viet Nam

Outline

Example: death after HIV infection



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):

$$h(t) = \mathrm{P}(T = t | T \geq t) \qquad \textit{discrete}$$

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

Kaplan-Meier

year	0-1	1-2	2-3	3-4	4-5	5-6	6-7	Total
death	1	2	6	11	9	11	2	60
censor	5	9	6	6	9	12	4	86

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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.

oucru

wellcome

University of Oxford

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Assumption: censored individuals represented by those at risk

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- One-to-one relation via

$$\mathrm{P}(T > t) = \prod_{t_i \leq t} \{1 - h(t_i)\} \qquad \textit{discrete}$$

$$\mathrm{P}(T > t) = \exp\left\{ - \int_0^t h(u) du \right\} \qquad \textit{continuous}$$

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  - Cox model $h(t) = h_0(t) \exp\{\beta_1 X_1 + \ldots + \beta_p X_p\}$

Outline

What and how?

- What is a competing risk?

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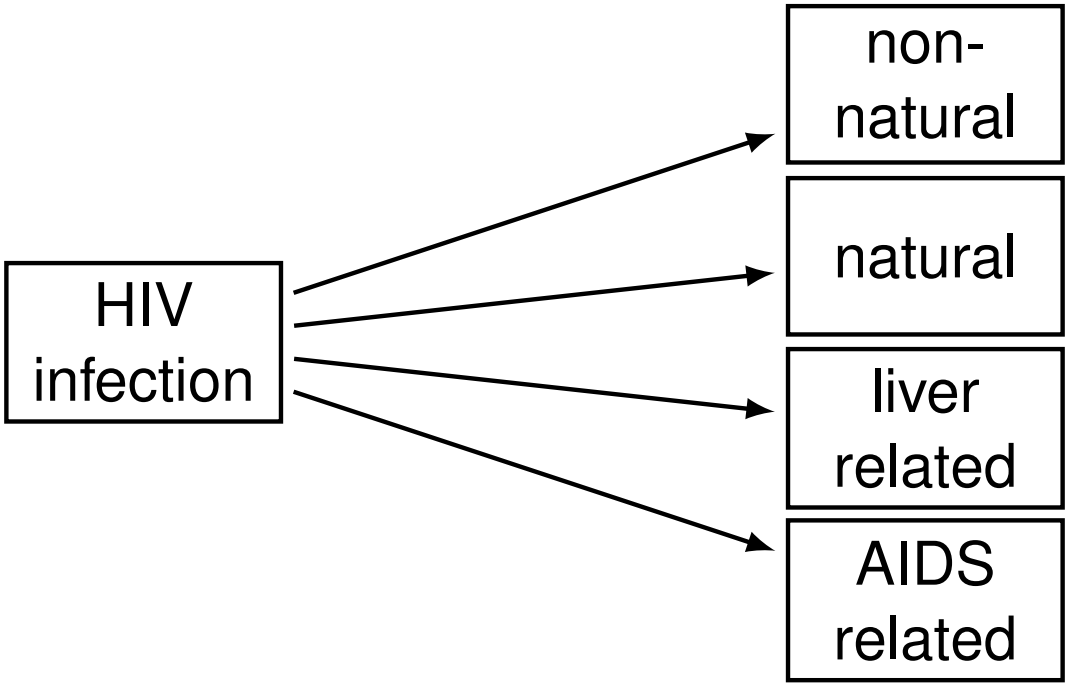
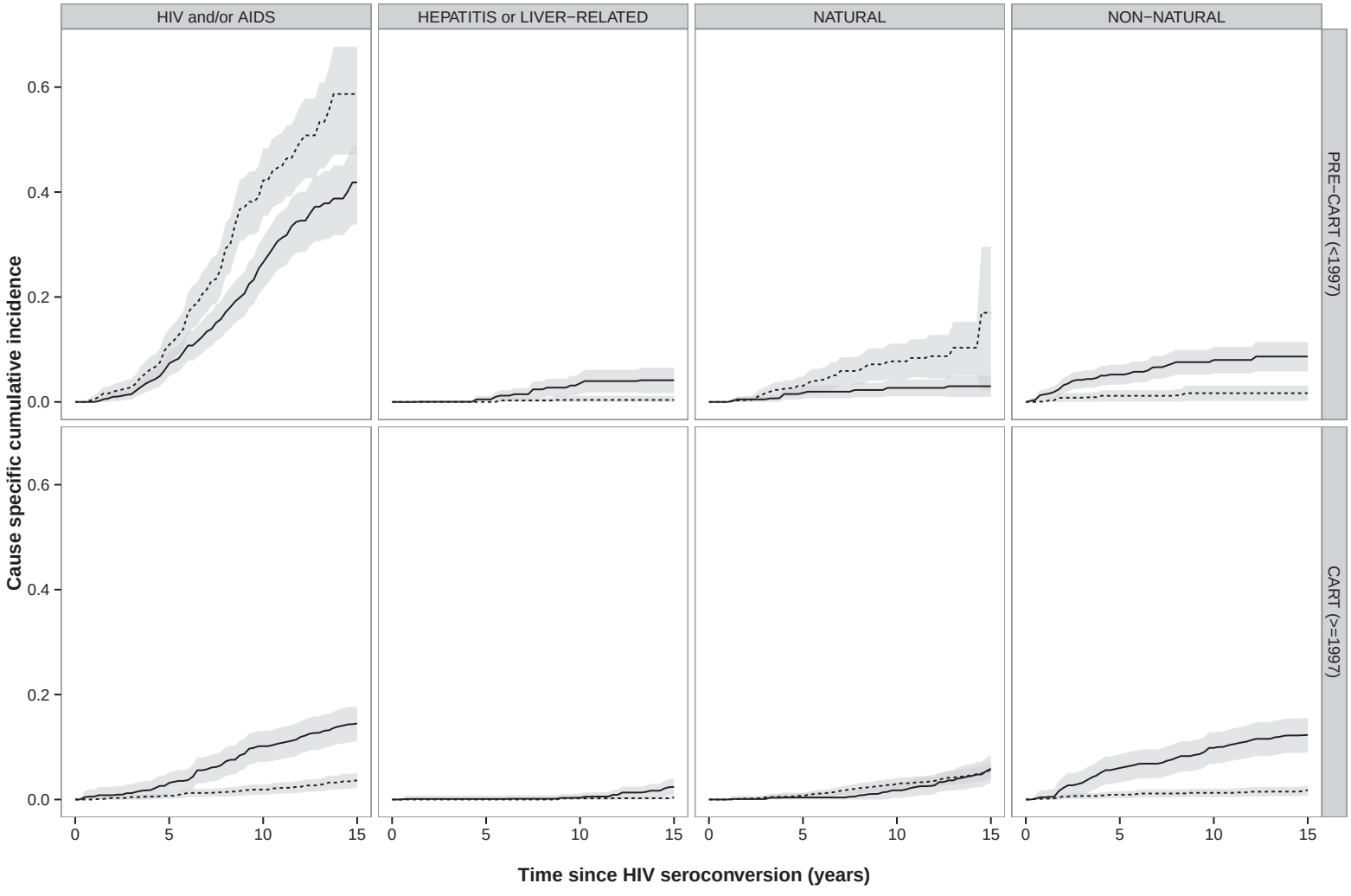
Example I: Causes of death (COD) after HIV infection



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

Cause-specific mortality by calendar period and hepatitis C status



Beyond classical survival analysis

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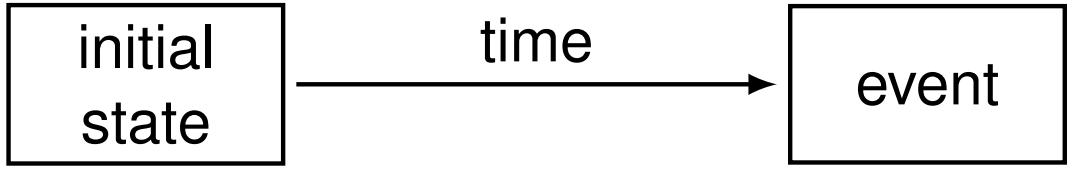

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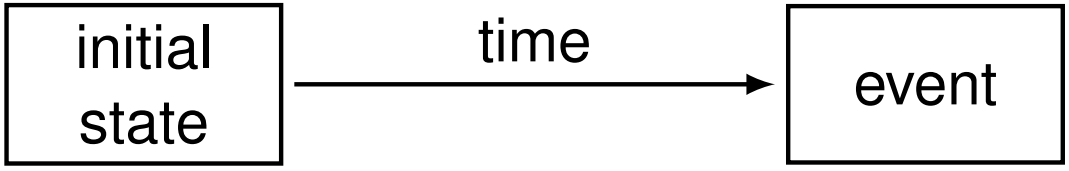

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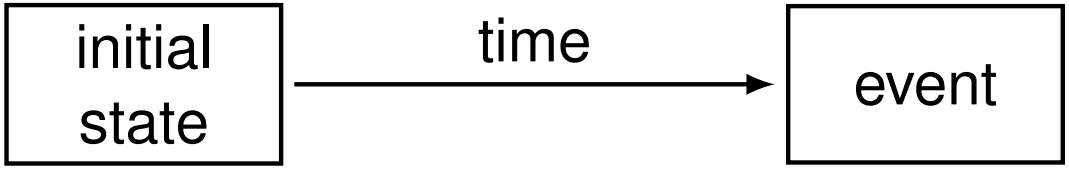

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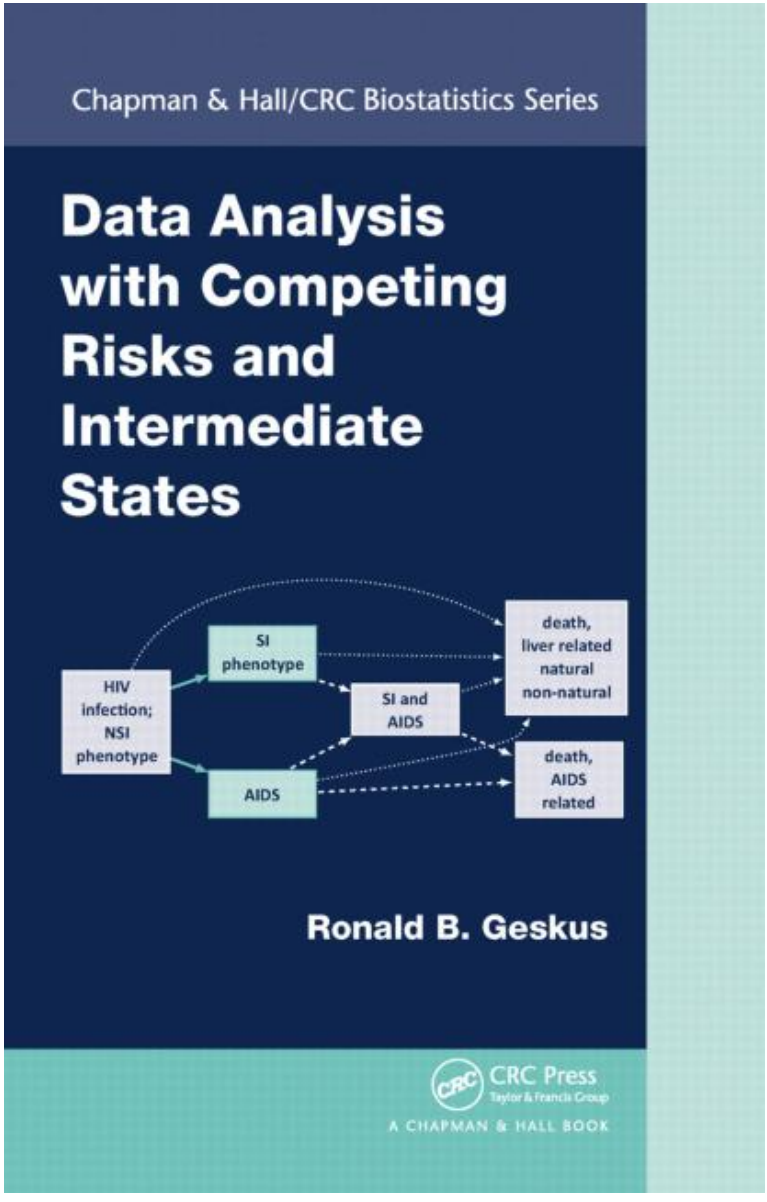
Published by CRC Press, 2015



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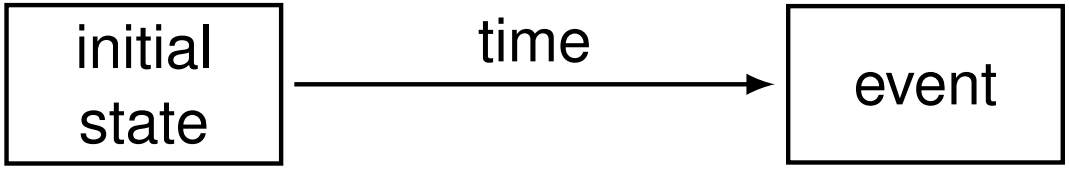

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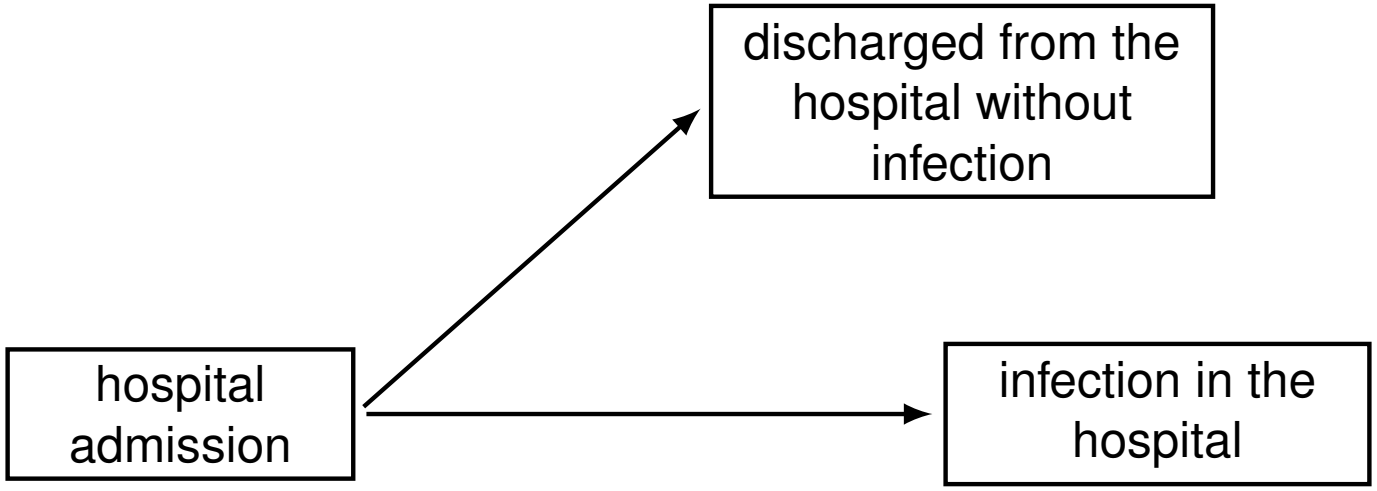
Outline

II: Time to staphylococcus infection during hospital stay



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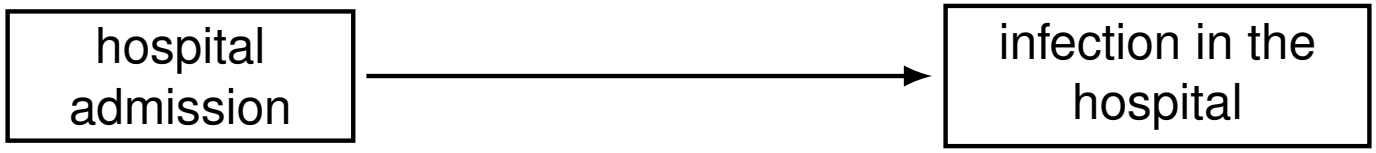

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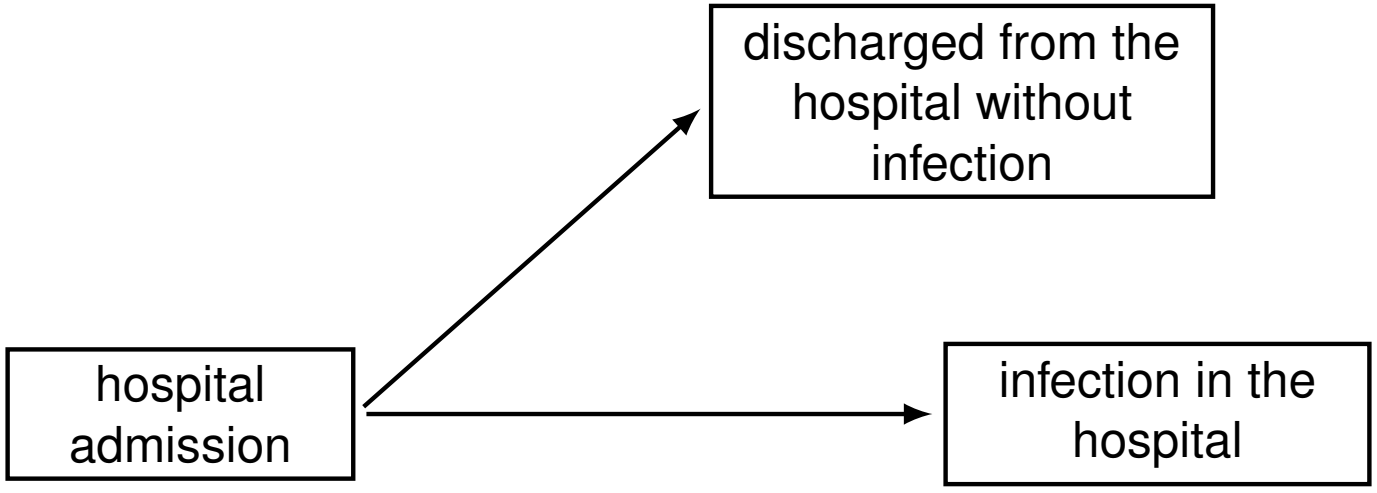

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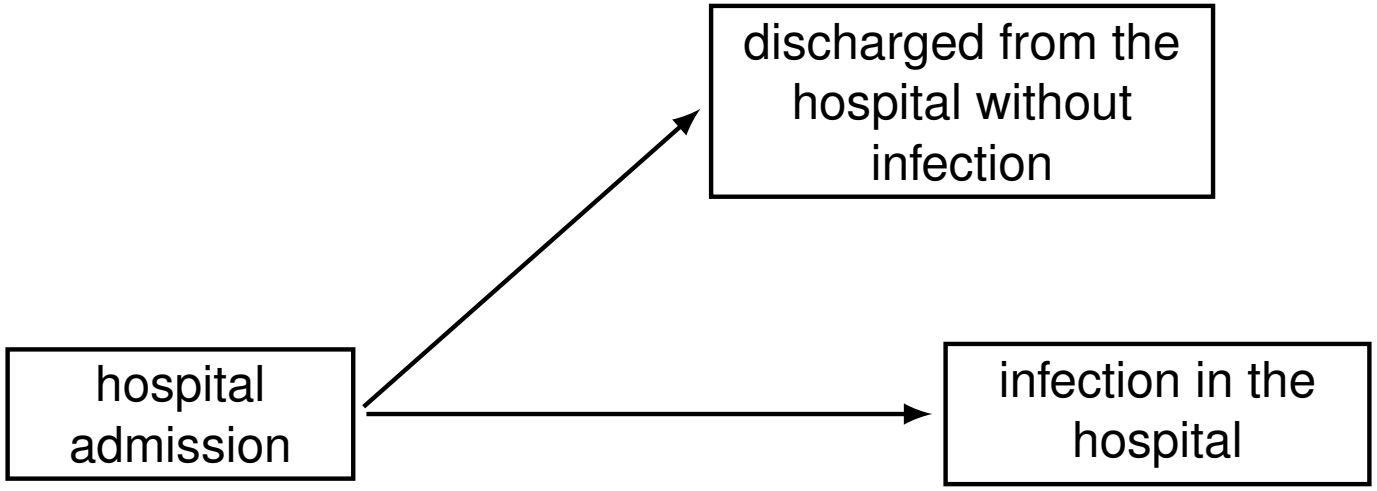

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- Net risk. Discharged individuals treated and interpreted as censored.

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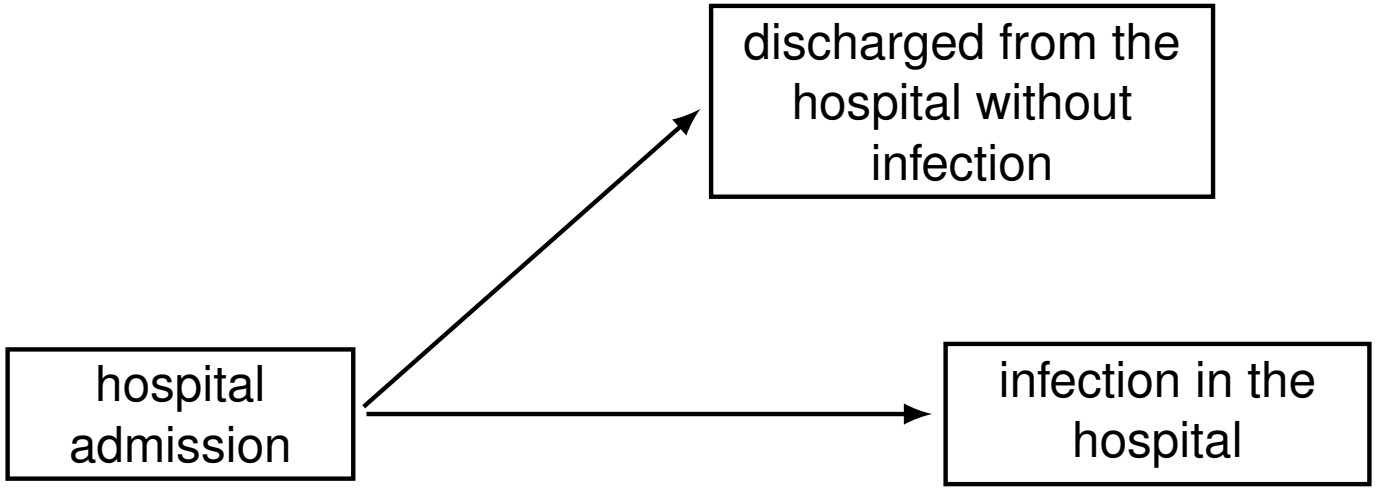

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- Which of two hospitals has higher risk may depend on type of question

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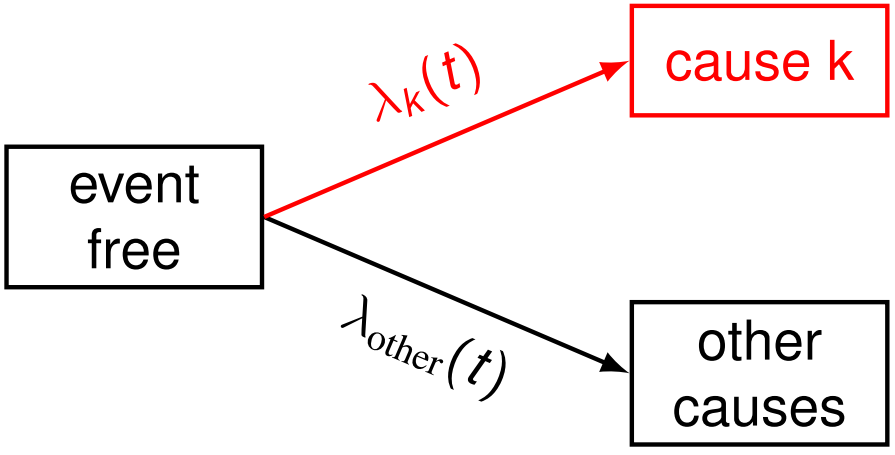
I: The multi-state approach: cause-specific hazard



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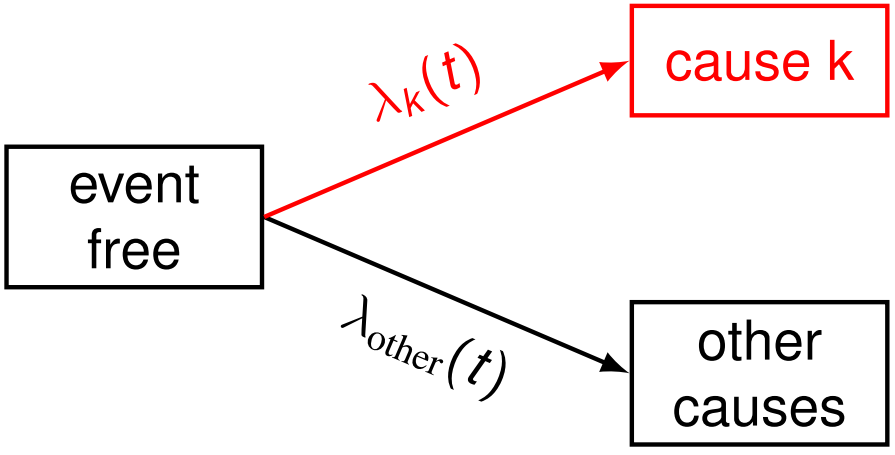

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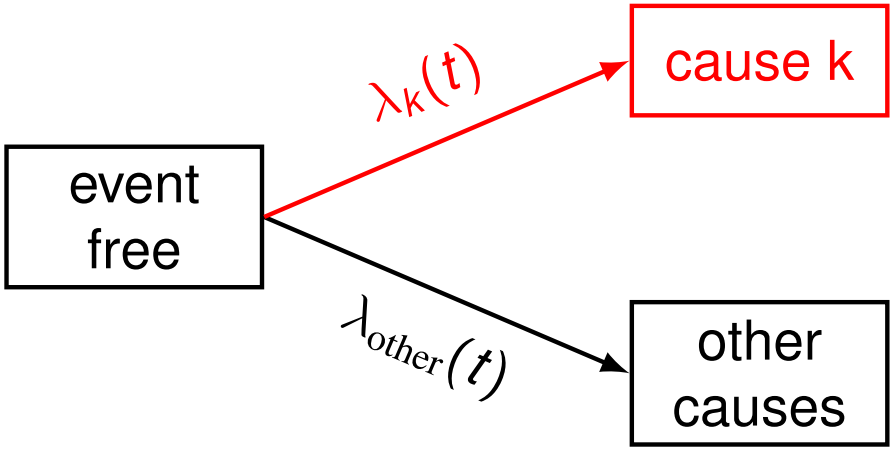

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- Risk $\mathrm{P}(T \leq t, E = k)$: Aalen-Johansen estimator;
  combines $\widehat{\lambda_k}(t)$ with Kaplan-Meier based on overall hazard
  $h(t) = \sum_{e=1}^{K} \lambda_e(t)$ (e.g. $K = 4$)

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- One-to-one relation with crude risk

$$\widehat{\mathrm{P}}(T_k^* > t) = \prod_{t_i \leq t} \left\{ 1 - \widehat{h_k}(t_i) \right\}$$

Outline

Regression on hazard

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  - Standard Cox model
  - Interpretation: cause-specific event rate among event-free individuals
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  - Not a marginal hazard, unless progression to competing risks unrelated
- Subdistribution hazard
  - Fine and Gray model: proportional subdistribution hazards
  - Interpretation: direct relation with cause-specific cumulative incidence

Outline

Rates and risks in competing risks setting

	hazard		cumulative
competing risks	marginal		net risk marginal survival function marginal cumulative incidence
	cause-specific	λ_k	no corresponding quantity
	subdistribution	h_k	crude risk $\mathrm{P}(T_k^* \leq t)$ cause-specific cumulative incidence
combined	overall	h	overall risk $\mathrm{P}(T \leq t)$ overall survival function overall cumulative incidence

Marginal distribution

- Hypothetical world in which competing events are absent
- Standard hazard estimate. Basis for Kaplan-Meier estimate of cumulative incidence/net risk

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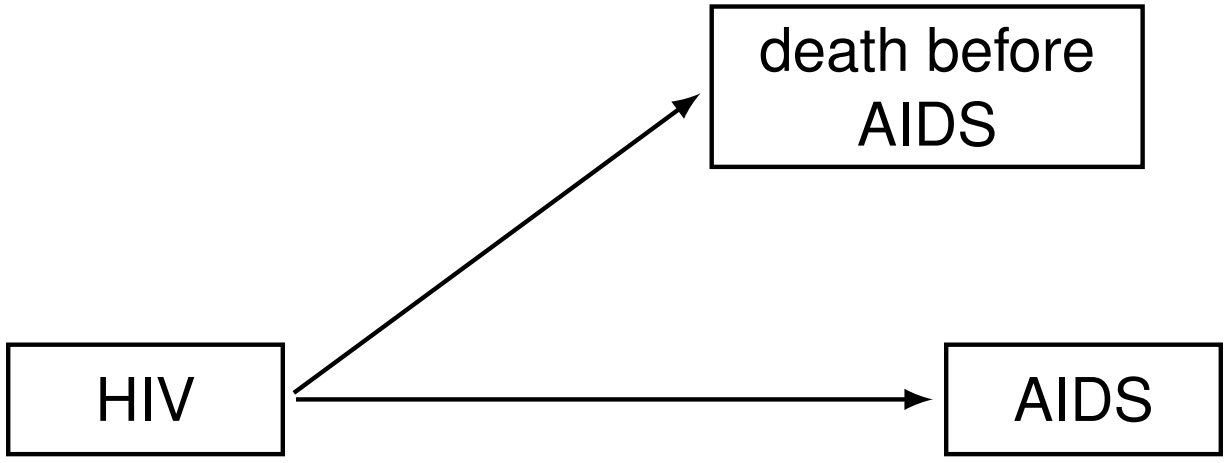
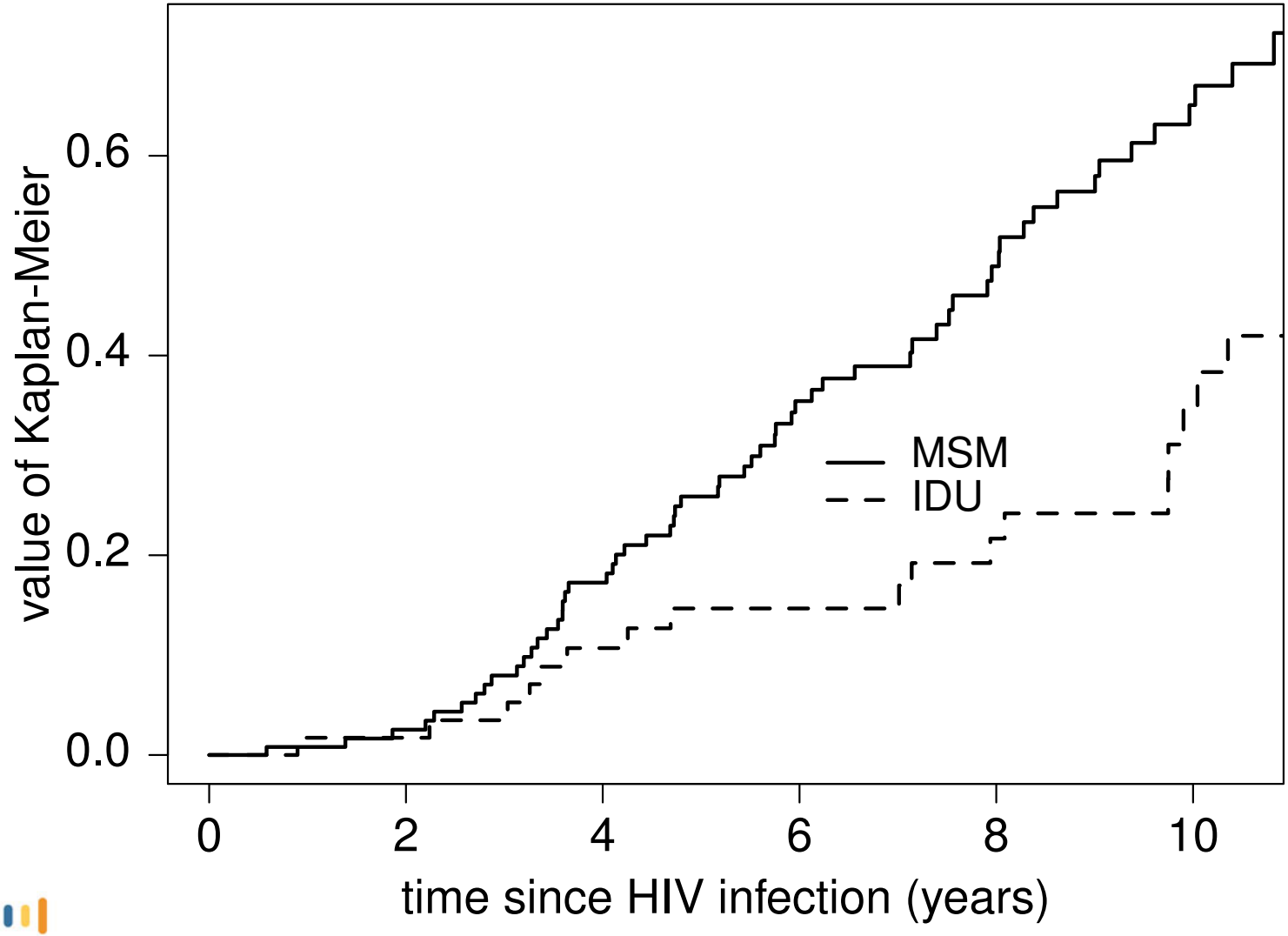
- Hypothetical world in which competing events are absent
- Standard hazard estimate. Basis for Kaplan-Meier estimate of cumulative incidence/net risk
- Assumption: Individuals that are censored can be represented by the ones that remain at risk. Mechanisms unrelated
- Otherwise: Kaplan-Meier has no meaning.
- Extra information may allow to show informative/dependent censoring, but independence can never be tested for

III: Time from HIV infection to AIDS



- Compare men who have sex with men (MSM) and injecting drug users (IDU)
- Interest in time to AIDS if there were no pre-AIDS death. Interest in etiology and marginal distribution
- Kaplan-Meier: censor at death (before AIDS)
  Assumption: those alive without AIDS represent pre-AIDS deaths

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



Explanation: dependent censoring

- 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, i.e. close to AIDS. Net risk estimate for IDU biased downwards

Rates and risks in competing risks setting

	hazard		cumulative	
competing risks	marginal		net risk	
			marginal survival function	
			marginal cumulative incidence	
	cause-specific	λ_k	no corresponding quantity	
	subdistribution	h_k	crude risk	$\mathrm{P}(T_k^* \leq t)$
			cause-specific cumulative incidence	
combined	overall	h	overall risk	$\mathrm{P}(T \leq t)$
			overall survival function	
			overall cumulative incidence	

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- Individuals censored by competing event don't have to be represented by the ones that remain at risk.
  Other censoring must be independent
- Cause-specific hazard
  - Basis for Aalen-Johansen estimator of cause-specific cumulative incidence/crude risk

Competing risks

- Competing risk is seen as separate event
- Individuals censored by competing event don't have to be represented by the ones that remain at risk.
  Other censoring must be independent
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- Subdistribution hazard: one-to-one relation with crude risk

Marginal or competing risks?

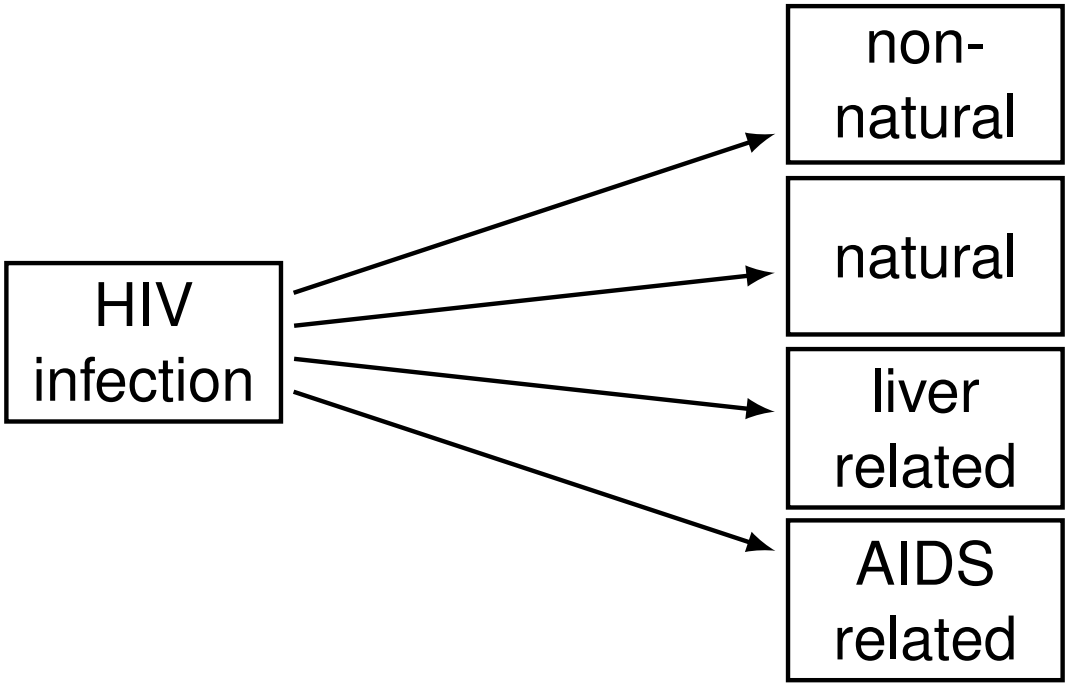
- Example I: spectrum in COD
  Competing risks; marginal analysis completely hypothetical
  No interest in change in AIDS-related death in world in which other COD's do not exist
- Example II: staphylococcus infection in hospital
  - Marginal: what if everyone would stay in hospital
  - Competing risks: how many infections are observed in hospital
- Example III: difference in natural history between IDU en MSM
  Marginal analysis (but not feasible with ACS data)

Outline

Which rate or risk?

- Both Cox model (cause-specific hazard) and Fine and Gray model (subdistribution hazard) make sense in presence of competing risks

Example 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)
- Different hazards can be chosen

Which rate or risk?

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- Example
  - AIDS-specific mortality reduced by cART
  - Other COD's: more frequent, even if cART has no side effects. No change in cause-specific hazard, but subdistribution hazard increases ("in the end we all die")
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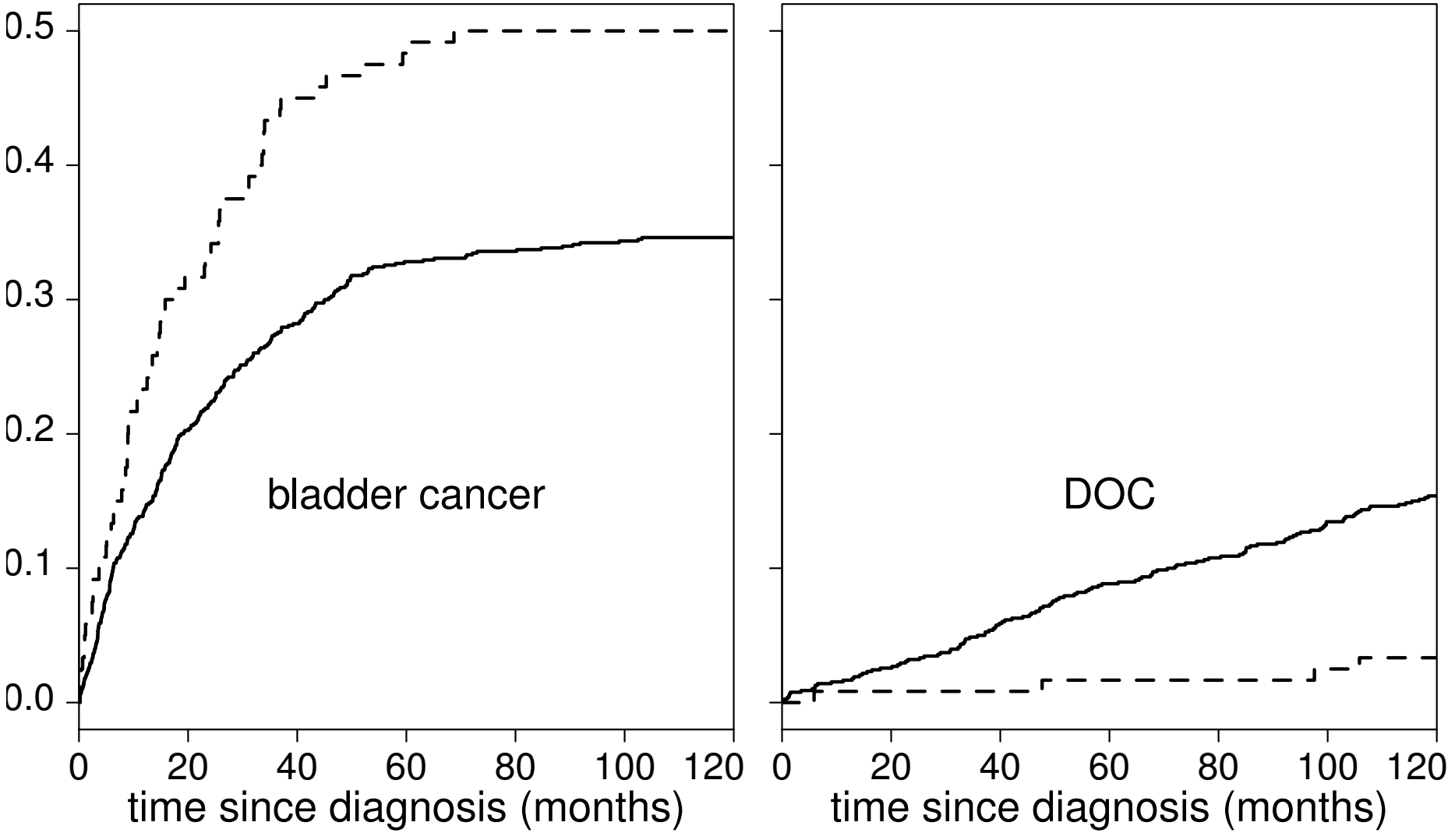
  - Subdistribution hazard includes impact on other event types
- Prediction: crude risk
  Based on regression model for cause-specific or subdistribution hazard, but only latter has one-to-one relation with cause-specific cumulative incidence/crude risk

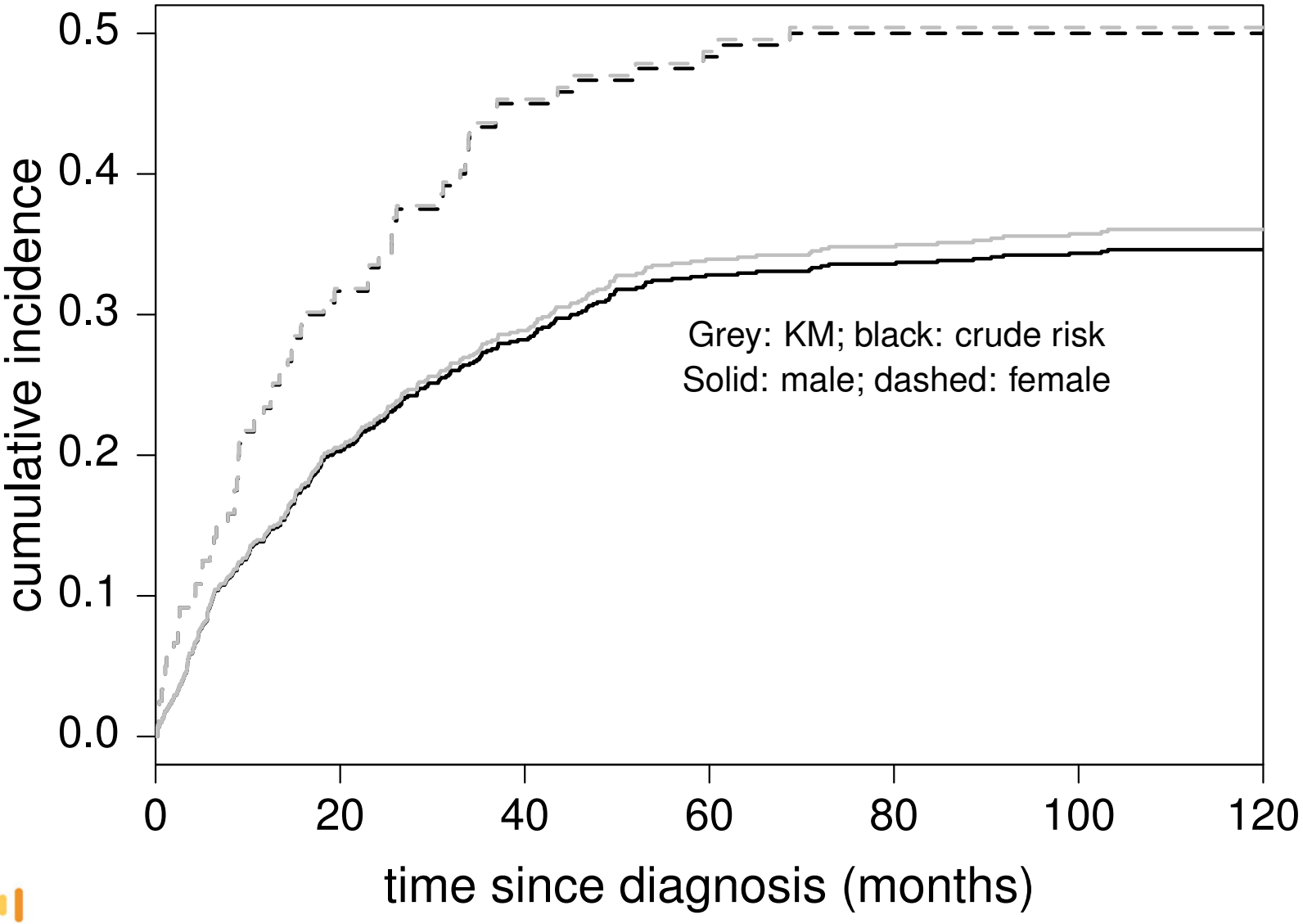
Outline

Bladder cancer; relapse, DOC competing



Left: relapse. Solid: male; dashed: female

Bladder cancer; relapse, DOC competing



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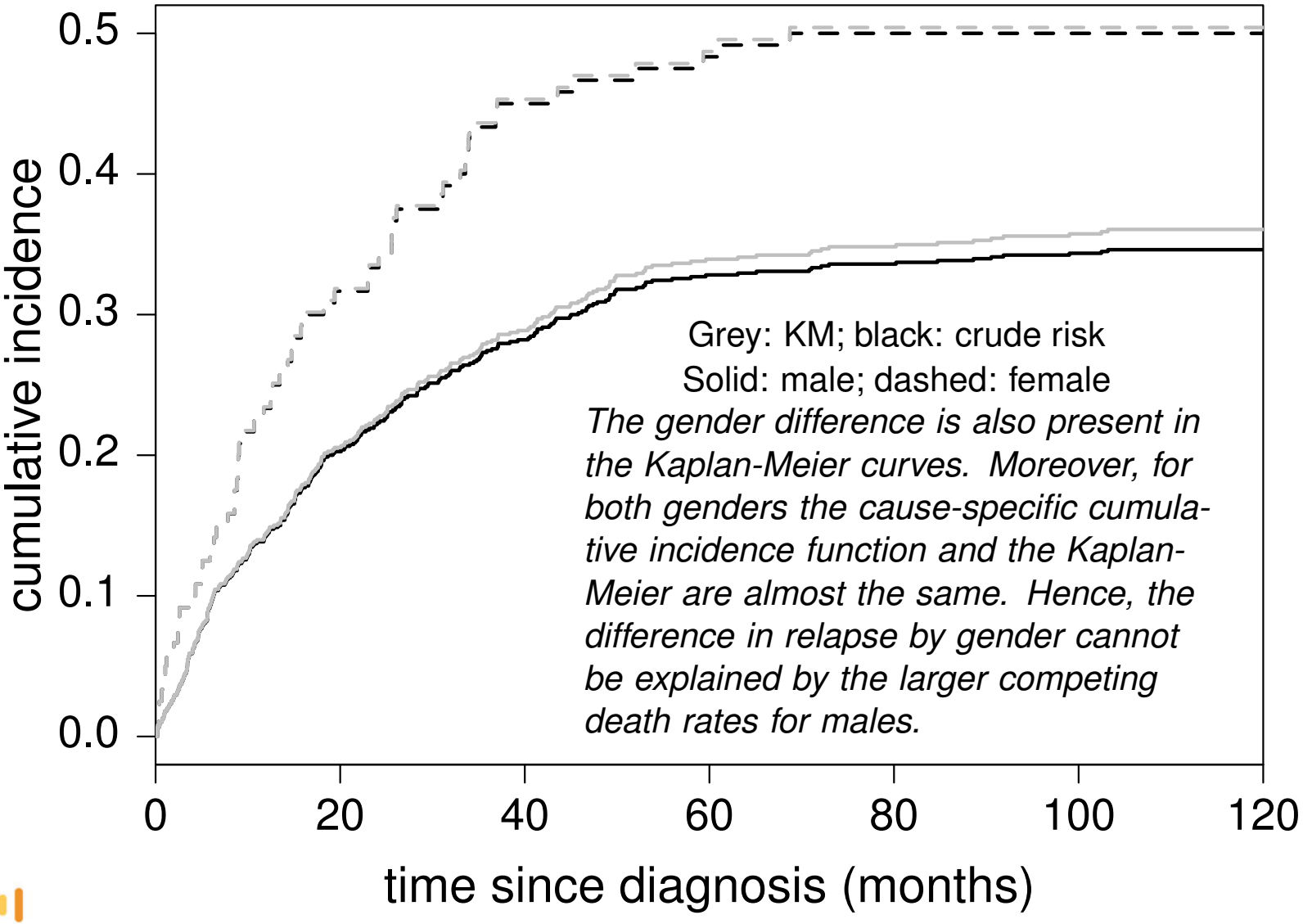

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- Estimates almost equal because there is little mortality due to other causes, at least during the first 40 months.
- If we combine both event times, the curves for males and females will become similar. Would estimate marginal hazard if every person 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.

THANKS!

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