

Analysing the causal effect of AIDS defining conditions on mortality, conditional on time varying covariates

Willem van der Wal, Ronald Geskus, Julia del Amo, Maria Prins, Santi Pérez-Hoyos

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Causal modelling

To Treat or Not To Treat: Evidence on the Prospects of Expanding Treatment to Drug-Involved Offenders

Sub-clinical Hypothyroidism...
To Treat Or Not?

Localized Prostate Cancer: To Treat Or Not To Treat?: The
European Association Of Urology (EAU) Lecture

Gestational Diabetes: To Treat or Not to Treat?

**Early-Stage Ovarian Cancer: To Treat or Not
To Treat**

To treat or not to treat, that is the question: proceedings of the Quebec Symposium for the
Treatment of Osteoporosis in Long-term Care Institutions, Saint-Hyacinthe, Quebec,

To Treat or Not to Treat

"...It is so natural for a doctor to feel the immediate need to intervene when seeing someone so ill, but this need to intervene is the reflection of your Western medical education.... It is so important to also consider what your actions will affect in the long run.

Nail Fungus: To Treat or Not to Treat?

To Treat or Not to Treat Euthyroid Autoimmune Disorder during Pregnancy?

To Treat or Not To Treat: Debating the Utility of
Antithrombotic Therapy in the Long-term Care Population

Counterfactuals

- Individual level:

$Y_{a=1}$, outcome for individual i when treated

vs.

$Y_{a=0}$, outcome for individual i when untreated

- Population level:

$P(Y_{a=1})$, outcome distribution when everybody treated

vs.

$P(Y_{a=0})$, outcome distribution when nobody treated

Marginal Structural Models

Marginal Structural Models (MSMs) model the population distribution of potential outcomes

e.g.

- time varying treatment

$$\lambda_{T_{\bar{a}}}(t) = \lambda_0(t) \exp\{\beta_1 A(t)\}$$

β_1 is causal hazard ratio

Fitting MSMs using Inverse Probability Weighting

Treatment A , outcome Y , confounder L :

- Weight each observation (A_i, Y_i) by $\frac{1}{P(A_i=a_i|L_i=l_i)}$
- In the weighted dataset, L does not predict A
- IPW with time varying treatment:

$$w_{ij} = \prod_{k=0}^j \frac{1}{P(A_{ik} = a_{ik} | \bar{A}_{ik-1} = \bar{a}_{ik-1}, \bar{L}_{ik} = \bar{l}_{ik})}$$

Conditional Effects

More specific causal questions:

“For patients with *poor health*, what is on average the difference in outcome between treating and not treating?”

And for patients with *good health*, what is on average the difference in outcome between treating and not treating?”

$$\rightarrow P(Y_a|V)$$

Condition e.g. on

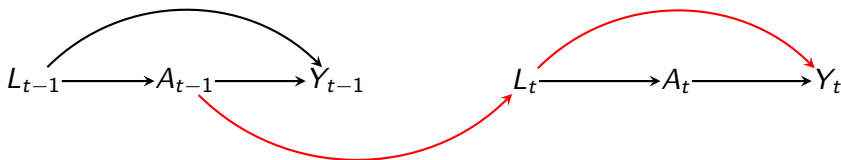
- baseline covariates
- follow-up time

Effect of $A(t)$ conditional on time varying covariates not possible using MSM!

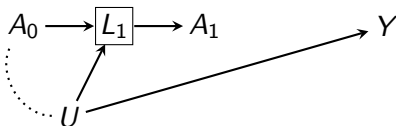
Adjusting away the effect

- Time dependent confounder and time dependent treatment
- Confounder also intermediary for treatment

→ Conditioning: indirect effect is “adjusted away”



Berkson's bias



- Condition on L_1
- An association between A_0 and U is introduced
- Therefore, an association between A and Y is introduced

History Adjusted Marginal Structural Models

- Condition on time varying variables by fitting MSM at each time point j
- Within each MSM, $L(j)$ is "baseline" covariate
- Example: compare mortality between treatment/no treatment in HIV patients, within 5 years after each time point, conditional on virus mutations at time point j

Maya L. Petersen and Mark J. van der Laan, "History-Adjusted Marginal Structural Models: Time-Varying Effect Modification" (April 2005). U.C. Berkeley Division of Biostatistics Working Paper Series. Working Paper 173.
<http://www.bepress.com/ucbbiostat/paper173>

Effect of ADCs on mortality

- Data from the CASCADE collaboration ($n = 14171$, 2121 events)
- Difference in mortality risk between *first ADC's*:
 - 0 AIDS-free
 - 1 TB
 - 2 Kaposi's sarcoma
 - 3 Esophageal candidiasis and Pneumocystis carinii pneumonia
 - 4 other opportunistic infections
 - 5 non-Hodgkin lymphoma and invasive cervical cancer
- Confounders: CD4 count, HIV RNA level, HAART use
- Condition on: HAART use, calendar time

Possible counterfactual treatment histories

e.g.

$$\bar{a} = 0, 0, 0, 0$$

$$\bar{a} = 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0$$

$$\bar{a} = 0, 0, 0, 0, 1, 1, 1, 1, 1, 1$$

$$\bar{a} = 0, 0, 0, 0, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2$$

$$\bar{a} = 3, 3, 3, 3, 3, 3, 3, 3,$$

$$\bar{a} = 0, 4$$

$$\bar{a} = 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 5, 5$$

Approach

MSM

- Stratify on availability of HAART (baseline)
- Two groups:
 - Included before 1997 → censored at 1997
 - Seroconverted in or after 1997

Model

$$\lambda_{T_{\bar{a}}}(t|B) = \lambda_0(t) \exp\{\beta_1 A(t) + \beta_2 B + \beta_3 A(t) \times B\}$$

- With:

λ = hazard of death

$T_{\bar{a}}$ = time of death for counterfactual ADC history \bar{a}

t = follow-up time

B = availability of HAART (0/1)

A = AIDS-defining condition (factor, reference is no ADC)

- Adjusted for gender, age, CD4, HAART and calendar time using IPW

Results

ADC category	HR	p	2.5%	97.5%
No ADC, <1997	1.00			
TB, <1997	21.57	0.00	9.66	48.14
KS, <1997	22.97	0.00	15.33	34.42
EC&PCP, <1997	21.92	0.00	12.63	38.04
Other OI's, <1997	19.66	0.00	8.59	44.97
NHL&ICC, <1997	63.72	0.00	33.97	119.54
No ADC, ≥1997	1.00			
TB, ≥1997	5.14	0.00	3.05	8.68
KS, ≥1997	2.70	0.04	1.07	6.80
EC&PCP, ≥1997	4.02	0.00	2.55	6.34
Other OI's, ≥1997	6.87	0.00	4.27	11.07
NHL&ICC, ≥1997	13.33	0.00	7.68	23.13

Approach

MSM

- Calendar time as time varying covariate
- Calendar time is *exogenous*
 - No risk of “adjusting away” the effect of ADCs
 - No risk of Berkson’s bias

Model 2

$$\lambda_{T_{\bar{a}}}(t|C(t)) = \lambda_0(t) \exp\{\beta_1 A(t) + \beta_2 C(t) + \beta_3 A(t) \times C(t)\}$$

- With:

λ = hazard of death

$T_{\bar{a}}$ = time of death for counterfactual ADC history \bar{a}

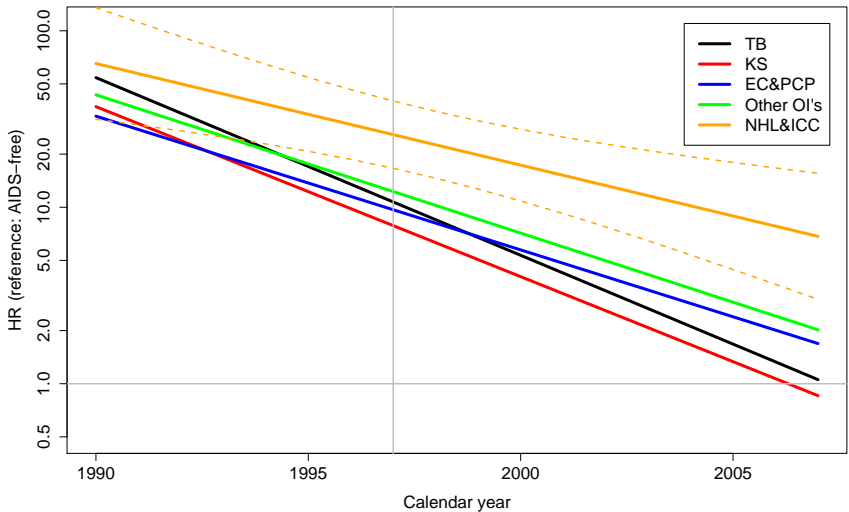
t = follow-up time

C = calendar time

A = AIDS-defining condition (factor, reference is no ADC)

- Adjusted for gender, age, CD4, HAART and calendar time using IPW

Results 2



Approach

HA-MSM

- Calendar time and individual HAART use as time varying covariates
- HAART use can be intermediate for the effect of ADC's

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HA-MSM

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→ Trick:

- At each time point j , build dataset consisting of measurements from j up to 5 years later
- Combine separate datasets, fit HA-MSM
- HA-MSM models mortality for different ADCs within 5 years from each time point, conditional on calendar time and individual HAART use at each time point

Model

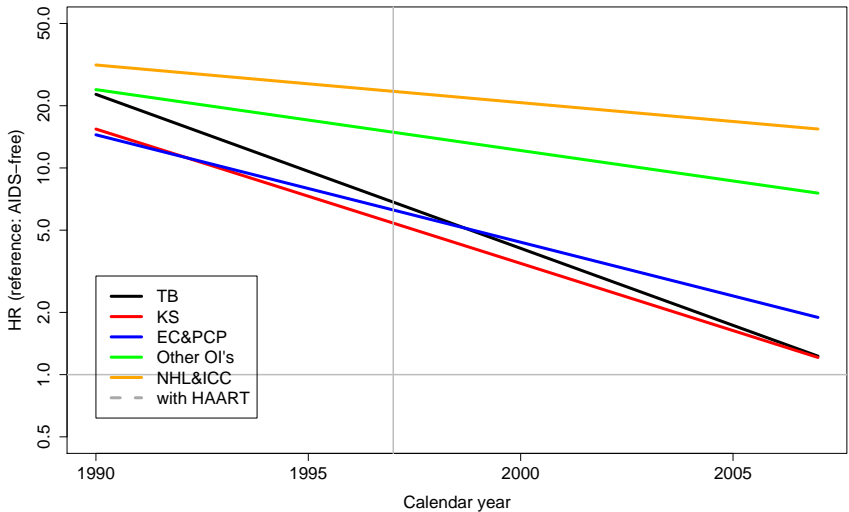
$$\lambda_{T_{\bar{A}(j-1)=0, \underline{a}(j, \dots, j+5)}}(j+t | C(j), H(j)) =$$

$$\lambda_0(t) \exp\{\beta_1 j + \beta_2 A(t) + \beta_3 C(j) + \beta_4 H(j) + \beta_5 A(t) \times C(j) + \beta_6 A(t) \times H(j)\},$$

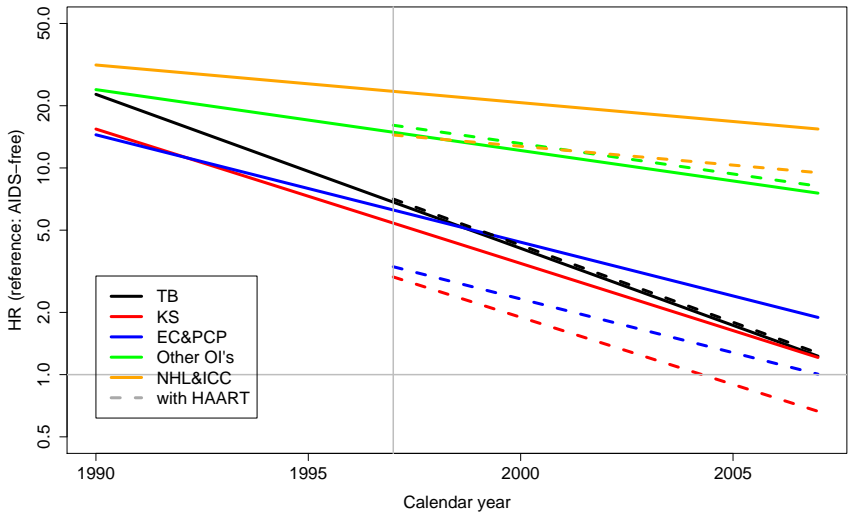
$$j = 0, \dots, n_i \quad , \quad 0 \leq t \leq 5$$

- With:
 - λ = hazard of death
 - T = time of death for counterfactual ADC history $\underline{a}(j, \dots, j+5)$, given $A(j-1) = 0$
 - C = calendar time
 - H = HAART use
 - A = AIDS-defining condition (factor, reference is no ADC)
- Adjusted for gender, age, CD4, HAART and calendar time using IPW

Results



Results



Discussion

- MSMs: why not condition on exogenous time varying covariate?
- HA-MSM: after time point j , $H(j)$ and $C(j)$ are not constant!
- Nonlinear effects? (But: large dataset!)