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

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Overview

- Causal modelling
- Effect of AIDS defining conditions (ADCs) on mortality in HIV patients
- Marginal Structural Model 1
- Marginal Structural Model 2
- History Adjusted-Marginal Structural Model
- Discussion
Causal modelling

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

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,

Nail Fungus: To Treat or Not to Treat?
Counterfactuals

- **Individual level:**
  \[ Y_{a=1}, \text{outcome for individual } i \text{ when treated} \]
  \[ \text{vs.} \]
  \[ Y_{a=0}, \text{outcome for individual } i \text{ when untreated} \]

- **Population level:**
  \[ P(Y_{a=1}), \text{outcome distribution when everybody treated} \]
  \[ \text{vs.} \]
  \[ P(Y_{a=0}), \text{outcome distribution when nobody treated} \]
Marginal Structural Models (MSMs) model the population distribution of potential outcomes.

e.g.

- **time varying treatment**

\[
\lambda_{T^a}(t) = \lambda_0(t) \exp\{\beta_1 A(t)\}
\]

- \(\beta_1\) 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:

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

\[ P(Y_a|V) \]

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”

\[
L_{t-1} \rightarrow A_{t-1} \rightarrow Y_{t-1} \\
L_t \rightarrow A_t \rightarrow Y_t
\]
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 $j$

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.
\[ \bar{a} = 0, 0, 0, 0 \]
\[ \bar{a} = 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0 \]
\[ \bar{a} = 0, 0, 0, 0, 1, 1, 1, 1, 1, 1 \]
\[ \bar{a} = 0, 0, 0, 0, 2, 2, 2, 2, 2, 2, 2 \]
\[ \bar{a} = 3, 3, 3, 3, 3, 3, 3, 3 \]
\[ \bar{a} = 0, 4 \]
\[ \bar{a} = 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 5, 5 \]
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:
  \( \lambda \) = 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

<table>
<thead>
<tr>
<th>ADC category</th>
<th>HR</th>
<th>p</th>
<th>2.5%</th>
<th>97.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ADC, &lt;1997</td>
<td>1.00</td>
<td>0.00</td>
<td>9.66</td>
<td>48.14</td>
</tr>
<tr>
<td>TB, &lt;1997</td>
<td>21.57</td>
<td>0.00</td>
<td>9.66</td>
<td>48.14</td>
</tr>
<tr>
<td>KS, &lt;1997</td>
<td>22.97</td>
<td>0.00</td>
<td>15.33</td>
<td>34.42</td>
</tr>
<tr>
<td>EC&amp;PCP, &lt;1997</td>
<td>21.92</td>
<td>0.00</td>
<td>12.63</td>
<td>38.04</td>
</tr>
<tr>
<td>Other OI’s, &lt;1997</td>
<td>19.66</td>
<td>0.00</td>
<td>8.59</td>
<td>44.97</td>
</tr>
<tr>
<td>NHL&amp;ICC, &lt;1997</td>
<td>63.72</td>
<td>0.00</td>
<td>33.97</td>
<td>119.54</td>
</tr>
</tbody>
</table>

| No ADC, ≥1997         | 1.00| 0.00| 3.05  | 8.68   |
| 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

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

- With:
  - \( \lambda \) = 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

The diagram illustrates the hazard ratio (HR) for AIDS-free survival over calendar years from 1990 to 2005. The X-axis represents the calendar year, and the Y-axis represents the HR (reference: AIDS-free). Different conditions are shown with distinct colors:

- **TB** (black line)
- **KS** (red line)
- **EC&PCP** (blue line)
- **Other OI's** (green line)
- **NHL&ICC** (orange line)

Each condition shows a decline in HR over time, indicating a reduction in mortality risk associated with these conditions as the epidemic progresses.
**HA-MSM**

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

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

→ 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

\[ \lambda_{T_{A(j-1)=0, a(j,\ldots,j+5)}}(j + t| C(j), H(j)) = \lambda_0(t) \exp\{\beta_1 j + \beta_2 A(t) + \beta_3 C(j) + \beta_4 H(j) + \beta_5 A(t) \times C(j) + \beta_6 A(t) \times H(j)\}, \]

\[ j = 0, \ldots, n_i, \quad 0 \leq t \leq 5 \]

- With:
  - \( \lambda \) = hazard of death
  - \( T \) = time of death for counterfactual ADC history
  - \( a(j,\ldots,j+5) \), 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

The graph shows the hazard ratio (HR) for various opportunistic infections (OIs) with and without HAART. The HR (reference: AIDS−free) for TB, KS, EC&PCP, Other OI's, and NHL&ICC are plotted from 1990 to 2005. The results indicate a significant decrease in the HR of these infections over time, particularly with the implementation of HAART.
Results

The figure shows the hazard ratio (HR) for various opportunistic infections (OIs) and HIV-related conditions over calendar years from 1990 to 2005, with a reference to AIDS-free status. The OIs and conditions include:

- TB
- KS
- EC&PCP
- Other OIs
- NHL&ICC
- with HAART

Each line represents the HR trend for a specific condition, with colors and line styles distinguishing between different conditions and the impact of HAART treatment. The HR values are shown on a logarithmic scale, indicating a significant reduction in mortality risk over time, particularly notable for conditions treated with HAART.
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!)