Time-dependent causal dose-response curves under limited data support – An example from HIV treatment research

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Background

Time-dependent causal dose–response curves, which plot the mean of the intervention-specific counterfactual outcome at time t as a function of different interventions through time t, can be used to summarize the effects of longitudinal interventions. Targeted maximum likelihood estimation is a viable option for estimation, though there is hardly any experience with it under long follow-up and limited support for a subset of intervention rules.

Data & Motivating Question

We use data from 7255 patients from 9 South African cohorts who started antiretroviral therapy between 2004-2017 and had (virological) failure (2 consecutive viral loads $>$ 1000 copies/mm^3) on first-line treatment and complete data at time of failure. We are interested in estimating the counterfactual survival probability at different follow-up times as a function of time of switch to second-line treatment regimens.

Methods

We compare two different approaches to estimate how the counterfactual probability of death 60 months after first-line failure varies as a function of the assigned switch time; that is, we compare survival for different treatment vectors $\mathbf{A} = (A_0, A_1, A_3, A_6, \ldots, A_{60})$ where second-line treatment ($A_t = 1$) is initiated at different time points st. We adjust for measured time-varying confounding of CD4 count, viral load and visit frequency (which are affected by past treatment status). The two approaches are:

i) we specify a marginal structural working model (MSM) which postulates a non-linear does-response relationship between follow-up time t, switch time st and the counterfactual probability of death,

$$\text{logit}(P(\text{Death(t)})^{\text{st}}) = \beta_0 + \beta_1 \log(t) + \beta_2(st - t) + \beta_3([st - t]^2) + \beta_4([st - t]^3) + \beta_5(\log(t) \cdot [st - t]) + \beta_6(\log(t) \cdot [st - t]^2)$$

and estimate it with (pooled) longitudinal targeted maximum likelihood estimation (LTMLE) as suggested by Petersen et al. (2014, *Journal of Causal Inference*) and implemented in the R-package `ltmle`;

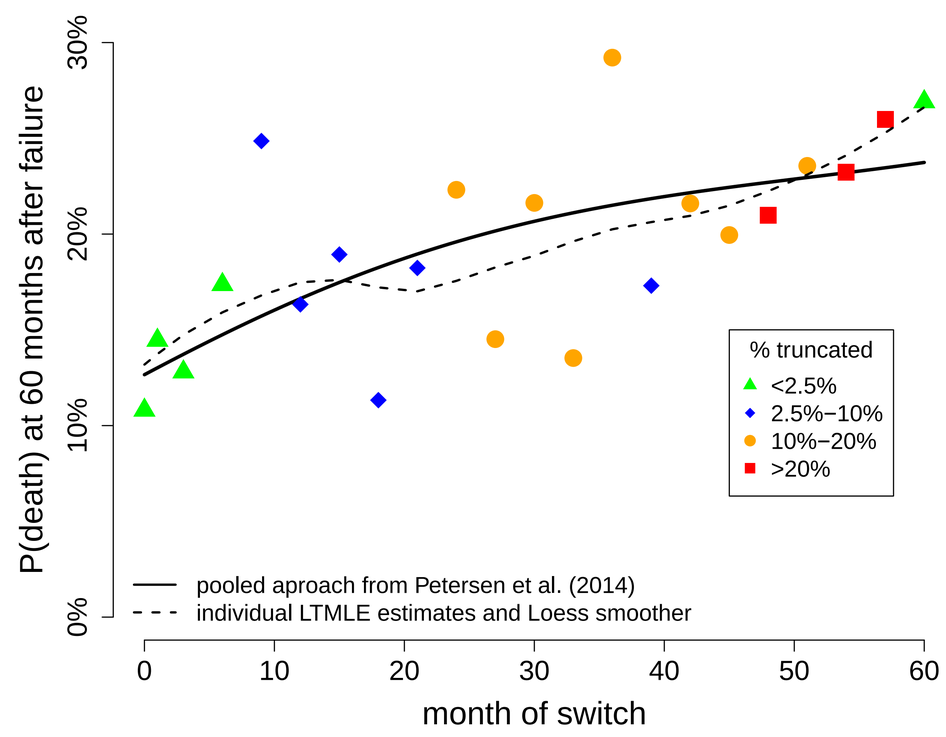
ii) we estimate the counterfactual probability of death 60 months after failure separately for each switch time (i.e. $\text{logit}(P(\text{Death(60)})^{\text{st}}), \text{st} \in (0, 1, 3, \ldots, 60)$) using LTMLE; and then graphically summarize the individual estimates with a Loess smoothing function.

The iterated outcome regressions for both approaches, i.e. the relationship between mortality and the covariates at each point in time were estimated using extensive super learning (with and without screening).

Results

The results are summarized in the Figure.

- The solid black line shows that approach i) suggests that a delay in switching increases mortality.
- The individual estimates (approach ii)) for each delay strategy (represented by coloured points) are highly variable. This is likely because there is limited data support for intervention strategies that delay switching by 12-57 months; in fact, for these strategies, $>$2.5% of cumulative inverse treatment and censoring probabilities, that are needed for the fitting process in i) and ii), are truncated, which suggests limited data support for these interventions and possible positivity violations. Nevertheless, the Loess smoother that summarizes the individual estimates (dashed line) yields a wobbly dose-response curve that is broadly in line with approach i).



Conclusions

LTMLE for longitudinal working MSM's can be useful, even when there is limited support for some intervention rules of interest. However, more work on the robustness of these approaches under limited data support and severe positivity violations is needed.

Acknowledgements, Affiliations & Contact

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