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Causal inference for survival and recurrent events with censored exposure : application to treatment of HIV/TB coinfection in Western Kenya

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Co-infection with HIV and tuberculosis (TB) is a significant public health problem in East Africa and much of the developing world. Very often, patients present at clinic with symptoms of TB and are found upon testing to also have HIV infection.

In the treatment of these patients, the timing of initiating combination antiretroviral treatment (cART) is a major concern. TB treatment must be started upon diagnosis ; however, many cART regimens have significant adverse drug interactions with early-phase TB therapy, and the added pill burden can reduce compliance with both treatments. These considerations have led to physicians delaying cART even when indicators of HIV disease stage warrant treatment.

Data from two randomized trials of early vs. late cART initiation are still limited, but preliminary results indicate that earlier initiation leads to reduced mortality. Our analysis is designed to investigate the issue using data on 8,810 HIV/TB co-infected patients in enrolled in the USAID-AMPATH Program in western Kenya ; specifically, our goal is to quantify the causal effect of cART initiation time on mortality and rate of opportunistic infection (OI).

Using observational data presents a number of challenges. In addition to nonrandom allocation of cART initiation, we must address drop out leading to censoring of exposure, outcome, or sometimes both. We use marginal structural hazard and rate models, fitted with IPW methods, to capture causal effects of cART initiation time on mortality and rate of OI recurrence. For those having missing exposure, we used the weight model to impute indicators of initiating cART at the remaining intervals. We also develop sensitivity analysis to assess the effect of key assumptions used in the imputations. Our method allows 763 individuals with missing treatment time to be included.

The fitted models suggest that hazard for death and recurrence of OI are substantially reduced by initiating cART early. Moreover, we demonstrate that analyses which exclude those with censored exposure times restricts the inference to a single direction that always favors later cART initiation times.

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